Guideline 2-29 Version 4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection

Members of the Gastrointestinal Cancer Disease Site Group

Guideline 2-29 Version 4 is comprised of 6 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/231

Section 1:	**Recommendations Summary (ENDORSED)**
Section 2:	**Guideline**
Section 3:	**Guideline Methods Overview**
Section 4:	**Evidence Review**
Section 5:	**Internal & External Review**
Section 6:	**Document Assessment and Review**

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For information about this document, please contact Dr. Brandon Meyers, the lead author, through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version 2008	1987 to 2007	Full Report	Web publication Clin Oncol. 2011;23(5):314-22	N/A
Version 2 September 2015	2007 to 2015	New data added to original full report	Updated web publication	See Appendix 8
Version 3 September 2019	2015 to 2018	New data found in Section 6: Document Assessment and Review (APPENDIX A)	Updated web publication	2015 recommendations are **ENDORSED**
Current Version 4 2024	2018 to 2023	New data found in Section 6: Document Assessment and Review	Updated web publication	2015 recommendations are **ENDORSED** with slight modification

Table of Contents

Guideline 2-29 Version 3: Section 1

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: Recommendations Summary

The 2015 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2023, and for details on how this guideline was ENDORSED.

GUIDELINE OBJECTIVES

To make recommendations with respect to the role of adjuvant systemic chemotherapy in stage II and III colon cancer patients who have undergone complete resection with curative intent.

TARGET POPULATION

The target population consists of adult patients with stage II and III colon cancer who have undergone complete resection with curative intent as primary therapy.

INTENDED USERS

Intended users of this guidance document are clinicians involved in the delivery of adjuvant systemic chemotherapy for stage II and III colon cancer patients.

RECOMMENDATIONS

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. While there is controversy about which tumour features 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 (MSI) or mismatch repair deficiency (dMMR).

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 on individual prognosis, and patient preferences.
- 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.

Recommendation 2

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

Qualifying Statements for Recommendation 2

- It would be reasonable to consider oxaliplatin-based chemotherapy for high-risk patients as part of an informed discussion between patients and their medical oncologists regarding treatment options.

Added to the 2019 Endorsement

- Additional evidence is expected that will inform decisions on duration of treatment with oxaliplatin-based treatment in patients with stage II disease. The following data are from a recent abstract (Iveson, ASCO 2018), and thus should be considered with caution. The IDEA collaboration evaluated 3 vs 6 months of therapy in a randomized, pre-planned, pooled analysis of 4 RCTs focusing on high-risk stage II patients. The decision to use CAPOX or FOLFOX was left to the treating physician. Noninferiority was not met for DFS comparing 3 vs 6 months (HR 1.18, 95% CI 1.05 to 1.31; noninferiority margin was 1.2). Five-year DFS was 80.7% vs 84.0% for 3 and 6 months, respectively. There was a significant reduction in grade 3 to 5 toxicity with 3 months of therapy (irrespective of regimen). See Appendix A for details.

Most patients suitable for oxaliplatin-based combination chemotherapy should discuss the differences between CAPOX and FOLFOX with their oncologist and choose a balance between efficacy and toxicity:

- The IDEA results suggest that 3 months of CAPOX results in very similar efficacy to 6 months, whereas it appears that 3 months of FOLFOX resulted in lower DFS (but the interaction test for duration and regimen was not statistically significant).
- The duration of 5-FU monotherapy was not addressed in IDEA, and should remain 6 months.

Recommendation 3

Adjuvant chemotherapy with a fluoropyrimidine monotherapy regimen following surgery in patients who have MSI/dMMR is not recommended. MSI/dMMR testing should be performed for all stage II patients for whom adjuvant chemotherapy is being considered. In stage II (in the absence of high-risk features) where a patient does not require adjuvant chemotherapy, MSI/dMMR testing is not recommended as it will not influence that decision.

Qualifying Statements for Recommendation 3

- In patients with high-risk stage II colon cancer (e.g., T4) ***and*** high MSI/dMMR status (a low risk factor), the choice of treatment is between observation and oxaliplatin-based chemotherapy, but data are lacking to guide this decision.

Stage III Colon Cancer

Recommendation 4

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

- Oxaliplatin-based chemotherapy
- Capecitabine
- 5-fluorouracil (5-FU) + leucovorin (LV)

Qualifying Statements for Recommendation 4

- 5-FU may be given intravenously in combination with LV and oxaliplatin in the regimens known as FOLFOX or FLOX, or capecitabine may be given orally in combination with intravenous oxaliplatin in the regimen known as CAPOX. These oxaliplatin-containing regimens have demonstrated superior overall survival when compared with 5-FU plus LV and are the recommended regimens. Oxaliplatin administration is associated with a 12.5% risk of severe neuropathy which is permanent in approximately 1% of patients. This needs to be considered in conjunction with the expected benefits of therapy.
- Owing to the toxicity profile of FLOX, it is used less frequently than FOLFOX.
- Some patients would not be considered appropriate for oxaliplatin-containing regimens. Examples include patients with underlying neurological 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 which has equivalent efficacy to intravenous bolus 5-FU/LV. Capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia but significantly more hand-foot syndrome when compared with bolus 5-FU/LV.
    - 5-FU in combination with LV
- Suitable patients should be offered entry into clinical trials testing new adjuvant treatments for resected stage III colon cancer.
- Patients have begun their adjuvant treatment within four to nine weeks of surgery in the adjuvant randomized controlled trials of resected colon cancer.

Added to the 2024 Endorsement

- In patients with high-risk stage III colon cancer ***and*** high MSI/dMMR status (a low risk factor), the choice of treatment is between observation and oxaliplatin-based chemotherapy, but data are lacking to guide this decision. See Section 6 for details.

Added to the 2019 Endorsement

- The IDEA collaboration evaluated 3 vs 6 months of therapy in a randomized, pre-planned, pooled analysis of 6 individual trials focusing on stage III patients. The treatment choice of CAPOX or FOLFOX was left to the treating physician. Overall, noninferiority was not met for 3 vs 6 months (3-year DFS HR 1.07, 95% CI 1.0 to1.15; noninferiority margin was 1.12). Pre-planned sub-group analysis revealed superiority for 6 months of FOLFOX, whereas 3 months of CAPOX was found to be noninferior to 6 months. 3 months of treatment was associated with lower rates of adverse events independent of chemotherapy regimen (Grothey et al, NEJM, 2018). An unplanned analysis was devised sub-dividing patients into “low” and “high” risk stage III disease, and is the basis for our statements below. See Appendix A for details.

    - Low-risk stage III (T1-3 N1):
      3 months of CAPOX is preferred over FOLFOX. Although the overall trial was negative for the primary endpoint, the shorter duration of treatment strikes a reasonable balance between efficacy and neurotoxicity of oxaliplatin (3 months noninferior to 6 months: HR 1.01, 95% CI 0.90 to 1.12). The pros and cons of 3 vs 6 months should be discussed with patients. Alternatively, 5-FU/capecitabine monotherapy for 6 months’ duration remains an option, especially for patients with contraindications to oxaliplatin or preferences for oral chemotherapy.

    - High-risk stage III (T4 +/- N2):

6 months of oxaliplatin-based chemotherapy (CAPOX or FOLFOX). Although the overall trial was negative for the primary endpoint, the shorter duration of treatment resulted in lower DFS (6 months superior to 3 months: HR 1.12, 95% CI 1.03 to 1.23). The longer duration of therapy is associated with higher rates of neurotoxicity. The pros and cons of CAPOX vs FOLFOX need to be discussed with patients.

Recommendation 5

Although post hoc analyses of studies have not shown a clear benefit of adjuvant fluoropyrimidine plus oxaliplatin regimens in patients older than 70 years of age, it is reasonable to consider oxaliplatin-based chemotherapy for patients older than 70 years as part of an informed discussion between patients and their medical oncologists regarding treatment options.

Added to the 2024 Endorsement

Qualifying Statements for Recommendation 5

- The Achieve trial in Japan indicated that age factor (<70 years versus ≥70 years) is not an effect modifier, but the data from the TOSCA trial in Italy supported that age is an effect modifier and stage III patients ≥70 years had worse PFS and worse OS outcomes than patients with <70 years. Thus, it requires more high-quality RCTs to investigate this issue in future research. See Section 6 for details.

Adjuvant Systemic Chemotherapy for Stage II and III Colon cancer Following Complete Resection: Guideline

The 2015 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2018, and for details on how this guideline was ENDORSED.

GUIDELINE OBJECTIVES

To make recommendations with respect to the role of adjuvant systemic chemotherapy in stage II and III colon cancer patients who have undergone complete resection with curative intent.

TARGET POPULATION

The target population consists of adult patients with stage II and III colon cancer who have undergone complete resection with curative intent as primary therapy.

INTENDED USERS

Intended users of this guidance document are clinicians involved in the delivery of adjuvant systemic chemotherapy for stage II and III colon cancer patients.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF 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. While there is controversy about which tumour features 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 (MSI) or mismatch repair deficiency (dMMR).

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 on individual prognosis, and patient preferences.
- While no separate overall survival (OS) data for high-risk versus low-risk stage II patients have been reported, a clinical rationale coupled with the methodological limitations of the existing studies led the Working Group to conclude that there may be a potential role for adjuvant chemotherapy for 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.

Key Evidence

- 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 over observation alone [1-4]. No separate OS data for high-risk and lower risk stage II patients were reported. These studies have an unclear risk of bias as all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias.

Recommendation 2

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

Qualifying Statements for Recommendation 2

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

Added to the 2019 Endorsement

- Additional evidence is expected that will inform decisions on duration of treatment with oxaliplatin-based treatment in patients with stage II disease. The following data are from a recent abstract (Iveson, ASCO, 2019), and thus should be considered with caution. The IDEA collaboration evaluated 3 vs 6 months of therapy in a randomized, pre-planned, pooled analysis of 4 RCTs focusing on high-risk stage II patients. The decision to use CAPOX or FOLFOX was left to the treating physician. Noninferiority was not met for DFS comparing 3 vs 6 months (HR 1.18, 95% CI 1.05 to 1.31; noninferiority margin was 1.2). Five-year DFS was 80.7% vs 84.0% for 3 and 6 months, respectively. There was a significant reduction in grade 3 to 5 toxicity with 3 months of therapy (irrespective of regimen). See Appendix A for details.

Most patients suitable for oxaliplatin-based combination chemotherapy should discuss the differences between CAPOX and FOLFOX with their oncologist and choose a balance between efficacy and toxicity:

- The IDEA results suggest that 3 months of CAPOX results in very similar efficacy to 6 months, whereas it appears that 3 months of FOLFOX resulted in slightly lower DFS (but the interaction test for duration and regimen was not statistically significant).
- The duration of 5-FU monotherapy was not addressed in IDEA, and should remain 6 months.

Key Evidence

- The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy demonstrated no difference with respect to OS in stage II patients in both the MOSAIC [5] and NSABP C-07 [6] trials. The MOSAIC subgroup analysis of low-risk and high-risk stage II patients demonstrated no significant benefit in OS for fluoropyrimidine plus oxaliplatin compared with 5-fluorouracil/leucovorin (5-FU/LV) alone. However, this trial was underpowered for this comparison. These studies have an unclear risk of bias as almost all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias.

Recommendation 3

Adjuvant chemotherapy with a fluoropyrimidine monotherapy regimen following surgery in patients who have MSI/dMMR is not recommended. MSI/dMMR testing should be performed for all stage II patients for whom adjuvant chemotherapy is being considered. In stage II (in the absence of high-risk features) where a patient does not require adjuvant chemotherapy, MSI/dMMR testing is not recommended as it will not influence that decision.

Qualifying Statements for Recommendation 3

- In patients with high-risk stage II colon cancer (e.g., T4) ***and*** high MSI/dMMR status (a low risk factor), the choice of treatment is between observation and FOLFOX but data are lacking to guide this decision.

Key Evidence

- One pooled analysis [7] demonstrated that OS was significantly worse in MSI/dMMR patients receiving adjuvant chemotherapy compared with those that had surgery alone.

Interpretation of Evidence for Stage II Colon Cancer – Recommendations 1-3

- There was agreement among the Working Group members that the overall certainty of the evidence was moderate.
- Although the Working Group looked at OS, disease-free survival, adverse events and quality of life, OS was considered to be the most important outcome, followed by adverse events. The Working Group was unanimous in their opinion that patients would also value the increased survival benefit of adjuvant chemotherapy, although patient input was not sought.
- The Working Group valued OS over toxicity when drafting the recommendations as they felt that the toxicities were manageable.
- The desirable effect (i.e., increased survival) is probably not large. The effect may be larger in high-risk stage II patients. At the same time, the undesirable effects are not small. The toxicity of the chemotherapy regimens need to be considered when deciding whether to administer adjuvant chemotherapy in stage II patients. The Working Group believed the desirable effect (longer survival) was largely relative to the undesirable effects (toxicity) in appropriately selected patients only.
- The evidence is not generalizable to the entire stage II population. It is unlikely that low-risk stage II patients will benefit from adjuvant chemotherapy at all.
- The Working Group believed that the effects of adjuvant chemotherapy in stage II colon cancer are not well studied and that the trials needed to determine the efficacy of adjuvant chemotherapy in this population may never be undertaken. The uncertainly with these data may never be resolved.

Stage III Colon Cancer

Recommendation 4

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

- FOLFOX or FLOX or XELOX
- Capecitabine
- 5-FU + LV

Qualifying Statements for Recommendation 4

- 5-FU may be given intravenously in combination with LV and oxaliplatin in the regimens known as FOLFOX or FLOX, or capecitabine may be given orally in combination with intravenous oxaliplatin in the regimen known as XELOX. These oxaliplatin-containing regimens have demonstrated superior OS when compared with 5-FU plus LV and are the recommended regimens. Oxaliplatin administration is associated with a 12.5% risk of severe neuropathy which is permanent in 1% of patients. This needs to be considered in conjunction with the expected benefits of therapy.
- Owing to the toxicity profile of FLOX, it is used less frequently than FOLFOX.
- Some patients would not be considered appropriate for oxaliplatin-containing regimens. Examples include patients with underlying neurological 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, which has equivalent efficacy to intravenous bolus 5-FU/LV. Capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia but significantly more hand-foot syndrome when compared with bolus 5-FU/LV.
    - 5-FU in combination with LV
- Suitable patients should be offered entry into clinical trials testing new adjuvant treatments for resected stage III colon cancer
- Patients have begun their adjuvant treatment within four to nine weeks of surgery in the adjuvant randomized controlled trials of resected colon cancer.

Added to the 2019 Endorsement

- The IDEA collaboration evaluated 3 vs 6 months of therapy in a randomized, pre-planned, pooled analysis of 6 individual trials focusing on stage III patients. The treatment choice of CAPOX or FOLFOX was left to the treating physician. Overall, noninferiority was not met for 3 vs 6 months (3-year DFS HR 1.07, 95% CI 1.0 to1.15; noninferiority margin was 1.12). Pre-planned sub-group analysis revealed superiority for 6 months of FOLFOX, whereas 3 months of CAPOX was found to be noninferior to 6 months. 3 months of treatment was associated with lower rates of adverse events independent of chemotherapy regimen (Grothey et al, NEJM, 2018). An unplanned analysis was devised sub-dividing patients into “low” and “high” risk stage III disease, and is the basis for our statements below. See Appendix A for details.

    - Low-risk stage III (T1-3 N1):
      3 months of CAPOX is preferred over FOLFOX. Although the overall trial was negative for the primary endpoint, the shorter duration of treatment strikes a reasonable balance between efficacy and neurotoxicity of oxaliplatin (3 months noninferior to 6 months: HR 1.01, 95% CI 0.90 to 1.12). The pros and cons of 3 vs 6 months should be discussed with patients. Alternatively, 5-FU/capecitabine monotherapy for 6 months’ duration remains an option, especially for patients with contraindications to oxaliplatin or preferences for oral chemotherapy.

    - High-risk stage III (T4 +/- N2):
      6 months of oxaliplatin-based chemotherapy (CAPOX or FOLFOX). Although the overall trial was negative for the primary endpoint, the shorter duration of treatment resulted in lower DFS (6 months superior to 3 months: HR 1.12, 95% CI 1.03 to 1.23). The longer duration of therapy is associated with higher rates of

neurotoxicity. The pros and cons of CAPOX vs FOLFOX need to be discussed with patients.

Key Evidence

- 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 [5] and XELOXA [8] trials. These studies have an unclear risk of bias as almost all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias.
- Two of the four [1,3,9,10] adjuvant fluoropyrimidine-based trials that reported comparative OS data for patients with stage III colon cancer demonstrated a benefit for 5-FU (with or without LV) over observation alone [3,9]. These studies have an unclear risk of bias as almost all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias.

- Oral capecitabine has equivalent efficacy with respect to OS to intravenous 5-FU/LV [11]. The other studies looking at this comparison do not report p-values [12-14] or do not report on the stage III patients separately [15]. These studies have an unclear risk of bias as almost all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias.

Recommendation 5

Although post hoc analyses of studies have not shown a clear benefit of adjuvant fluoropyrimidine plus oxaliplatin regimens in patients older than 70 years of age, it is reasonable to consider FOLFOX for patients older than 70 years as part of an informed discussion between patients and their medical oncologists regarding treatment options.

Key Evidence

- There was no OS benefit of adjuvant fluoropyrimidines plus oxaliplatin regimens in patients older than 70 years of age in any of three trials that performed this post hoc subgroup analysis [5,6, 8]. These studies have an unclear risk of bias as almost all domains in the Risk of Bias assessment were rated as either low or unclear risk of bias. Caution must be exercised when interpreting post hoc subgroup analyses.

Interpretation of Evidence for Stage III Colon Cancer – Recommendations 4 and 5

- There was agreement among the Working Group members that the overall certainty of the evidence was high except for the age data, which were considered to be of moderate certainty.
- Although the Working Group looked at OS, disease-free survival, adverse events and quality of life, OS was considered to be the most important outcome, followed by adverse events. The Working Group was unanimous in their opinion that patients would also value the increased survival benefit of adjuvant chemotherapy, although patient input was not sought. The Working Group valued OS over toxicity when drafting the recommendations as they believed that the toxicities were manageable given the increase in OS.
- The desirable effect (i.e., increased survival) is large. At the same time, the undesirable effects (toxicity) are manageable in this population. The Working Group believed the desirable effect (longer survival) is large relative to the undesirable effects (toxicity) in the selected group of stage III patients.

- The evidence is generalizable to the entire stage III population that is younger than 70 years of age. It is unlikely that evidence is generalizable to all patients older than 70 years, although it may be useful for those patients who are fit.
- The Working Group believed that there were no alternate interpretations of the evidence for adjuvant chemotherapy in stage III colon cancer patients.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered the recommendations provided above to be the current standard of care and, thus, would be feasible to implement and would not affect current health inequities. These recommendations would validate what healthcare providers are currently providing to their stage II and III colon cancer patients. The Working Group believed the outcomes valued in this guideline would align well with patient values and patients would view these recommendations as acceptable.

UPDATING

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

FUNDING

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.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix 2.

Disclaimer

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.

Contact Information

For information about this document, please contact Dr. Brandon Meyers, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline 2-29 Version 3: Section 3

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: Guideline Methods Overview

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2018, and for details on how this guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [16]. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [16,17]. PEBC guidelines include an evidence review (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

Justification for Guideline

In October 2013, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (DJ) reviewed and interpreted the new eligible evidence and proposed that the existing recommendations needed a full update.

Guideline Developers

This guideline was undertaken by the Gastrointestinal Disease Site Group (GI DSG). The group was comprised of 16 medical oncologists, nine radiation oncologists, seven surgical oncologists, and one PEBC methodologist. (see Appendix 1 for membership). The project was led by a small working committee of the group, referred to as the Working Group from this point forward, whose members were responsible for creating the evidence base, drafting the first version of the recommendations, and leading the response to the external review. The Working Group members are noted in Appendix 2. All members contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Competing interests in the areas of research grant and educational

grants were declared; Appendix 2 provides further detail. Individuals with competing interests were not allowed to participate as a member of the Working Group unless otherwise stated.

Guideline Methods

The PEBC uses the AGREE II as its organizational methodological framework. Beginning with a project plan, systematic methods of evidence synthesis and/or adaptation, consensus of interpretation of evidence, drafting and contextualization of recommendations, and external review of the draft guideline define key steps in the process. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

A search for existing guidelines for adaptation or endorsement was conducted. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument. A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4).

Using this evidence, recommendations were drafted and approved by the Stage II and III Colon Cancer Working Group. The draft document was circulated for internal review to an independent committee of the PEBC and for external review to experts in the field (see Section 5). Refinements to the document were made in response to the feedback received and final recommendations approved by the guideline group. To achieve approval of the draft document and final document, a consensus by 75% of the members of the Stage II and III Colon Cancer Expert Panel as well as the Targeted Peer Reviewers was required, with dissenting opinions noted, where appropriate.

Focus

The primary focus of this guideline is on the clinical evidence. Other features related to the implementation of recommendations such as costs, human resources, unique requirements for special or disadvantaged populations, and development and measurement of quality indicators are addressed by other divisions at Cancer Care Ontario. The perspective of the Stage II and III Colon Cancer Working Group on these issues is described in Section 2 under "Implementation Considerations".

Details

- Details of the evidence base can be found in the section labeled EVIDENCE (Section 4).
- Details of the internal and external reviews can be found in the section labeled REVIEW (Section 5).
- Details of the updating process can be found in the section labeled EVIDENCE (Section 4).

ACKNOWLEDGEMENTS AND AUTHORSHIP

The GI DSG and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Bill Evans, Donna Maziak, Sheila McNair and Hans Messersmith for providing feedback on draft versions.
- Judy Brown for conducting the document assessment and review of the original version of this guidance document.
- Kristy Yiu for conducting a data audit.
- Sara Miller for copyediting.

A complete list of the members of the GI DSG and the Working Group, with their affiliations and conflict of interest information, is provided in Appendix 2.

Guideline 2-29 Version 3: Section 4

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: Evidence Review

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INTRODUCTION

In Ontario, colorectal cancer is second only to lung cancer as a cause of cancer death, with an estimated 3400 deaths in 2014. Colorectal cancer is the third most common cancer site when both sexes are combined, representing 12.1% of all new cancer cases, with approximately 8900 new cases per year [18]. In males, colorectal cancer is the second most common site, and, in females, colorectal cancer is the third most common site [18].

The prognosis of the newly diagnosed colon cancer patient is determined by the clinico-pathological stage of the disease. In stage II disease, there is tumour penetration through the bowel wall beyond the submucosa, but there is no involvement of the regional lymph nodes or distant sites. Stage III disease involves metastases to regional lymph nodes. The overall survival (OS) of patients with stage II disease is 70% to 80% five years after surgery [19]. More than one-third of patients with colon carcinoma present with lymph node metastases (stage III), and more than one-half of those patients, initially treated for cure, relapse and later die of the disease. High-risk stage II disease is associated with an outcome similar to that of patients with stage III disease, with a five-year OS of 40% to 50%. The definition of "high risk" is a subject of considerable debate and research, and remains inadequately captured in current TNM staging (see Appendix 3 for a comparison of staging systems). Possible prognostic factors that may indicate a higher risk of recurrence include T4 stage, perforation at the site of the tumour, inadequately sampled lymph nodes, poor differentiation, and molecular markers such as microsatellite stability; however, these risk factors have not been confirmed in prospective studies.

Several guidelines on the use of adjuvant therapy for patients with stage II or III colon cancer have been published in the past. In 1990, a National Institute of Health Consensus Conference reviewed the available evidence and recommended adjuvant treatment with 5-fluorouracil (5-FU) and levamisole for patients with curatively resected stage III colon cancer [20]. Many questions remained about other therapies. In 2008, the Gastrointestinal Disease Site Group (GI DSG) developed a systematic review (SR) and clinical practice guideline on adjuvant systemic chemotherapy for stage II and III colon cancer following complete resection. The guideline recommended adjuvant chemotherapy for stage III patients [21]. For those 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 5-FU given intravenously in combination with leucovorin (LV) and oxaliplatin (FOLFOX or FLOX). Since the publication of the guideline in 2008, newer regimens have been assessed in this patient population and some older agents have been either abandoned because of non-effectiveness or replaced by more

efficacious agents. Therefore, the GI DSG determined that a full update of the original guideline was warranted.

Historical and Inactive Regimens in the Adjuvant Setting

Fluoropyrimidine plus levamisole is an active regimen in the treatment of colon cancer. However, this regimen is considered historical in that newer and more effective regimens are currently available. Therefore, this regimen will not be discussed in this iteration of this guideline document. Data for regimens and comparisons that are no longer considered relevant owing to lack of effectiveness (e.g., fluoropyrimidine plus mitomycin C; fluoropyrimidine plus nitrosoureas; fluoropyrimidine plus irinotecan, carmofur) will also not be discussed in this version of the guideline but can be found in the previous version of this guideline (available on request).

In order to make recommendations as part of a clinical practice guideline, the Working Group of the GI DSG developed this evidentiary base upon which those recommendations are based. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1) What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy versus observation on disease-free survival (DFS) and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

2) What is the impact of adjuvant intravenous (IV) 5-FU versus oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

3) **a)** What is the impact of adjuvant fluoropyrimidines versus fluoropyrimidines plus oxaliplatin on DFS and OS in patients with:

- **i)** stage II or III colon cancer who have undergone complete resection with curative intent?
- **ii)** stage II colon cancer who have undergone complete resection with curative intent?
- **iii)** stage III colon cancer who have undergone complete resection with curative intent?

b) 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?

4) **a)** What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?
b) What is the impact of adjuvant fluoropyrimidine monotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

5) 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

This evidence review was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing SRs: If one or more existing SR are identified that address the research questions and are of reasonable quality, then those SRs would form the core of the evidence review.
2. SR of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

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Search for Systematic Reviews

An overall search strategy was developed and implemented that captured both existing SRs and the primary literature in the following databases: MEDLINE, EMBASE, American Society for Clinical Oncology (ASCO) meeting abstracts, as well as European Society of Medical Oncology (ESMO)/European Cancer Congress (ECC) meeting abstracts. Identified SRs were further evaluated based on their clinical content and the similarity of the questions they addressed to the questions and objectives of this guideline. SRs that were found to be directly relevant to this guideline and, therefore, potential foundations for this evidence review, were assessed using the AMSTAR tool [22].

Search for Primary Literature

Below are methods for locating and evaluating primary literature if no existing SR were identified, or if identified reviews were incomplete in some fashion. If the identified SRs are incomplete, then the primary literature review might be reduced in scope (e.g., subject areas covered, time frames covered).

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 (ASCO) (1998 to 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 evidence contained within the original PEBC guideline on adjuvant chemotherapy for stage II and III colon cancer. In addition, ASCO and ESMO/ECC meeting abstracts were searched for the period since September 2007. Reference lists of included studies were also searched. The full literature search was the same as the original literature search and can be found in Appendix 4.

Study Selection Criteria and Process

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

1. They were fully published reports or published abstracts of randomized controlled trials (RCTs) or fully published reports of 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 comparisons listed in the guideline questions.
2. The primary outcome of interest was DFS. Secondary outcomes of interest were OS, treatment toxicity, and quality of life. Articles had to report data for one of these outcomes. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.
3. They were English-language publications.
4. The clinical trials were published after 1987. Buyse et al. [23] summarized the results of randomized trials of adjuvant therapy for colorectal cancer up to 1987. The results of this meta-analysis are reviewed at the beginning of the Results section.

Exclusion Criteria

Letters, editorials, notes, case reports, and commentaries were not eligible.

A review of the titles and abstracts that resulted from the search was done by one reviewer (JB) independently during the document assessment and review of the 2008 guideline. For those items that warranted full-text review, two reviewers evaluated each item independently (JB, RC).

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from studies found in the updated literature search were extracted by one member of the Working Group (RC).

Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating benefit for the experimental group for a given outcome. All extracted data and information were audited by an independent auditor.

Important quality features, such as generation of allocation sequence, allocation concealment, blinding, intention-to-treat (ITT) analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination, were extracted for each study. Risk of bias was also assessed for each included trial http://handbook.cochrane.org/ (Part 2, Section 8.5). SRs, with or without meta-analyses, were assessed using the AMSTAR instrument [22].

Synthesizing the Evidence

Meta-analysis was not planned owing to the variety of regimens used in the trials relevant for each question.

RESULTS

Literature Search Results – Original Version 1

Meta-analysis of Adjuvant Therapy (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) [23]. Seventeen trials compared adjuvant chemotherapy with surgery alone in patients with colorectal cancer (6791 patients). The pooled results detected no significant difference in the odds of death (mortality odds ratio [OR]) between treatment and control (OR, 0.96; 95% confidence interval [CI], 0.87 to 1.06). Stage could not be examined due to the lack of standardization of staging methods. For the subgroup of patients treated with 5-FU for at least one year, a significant decrease in the odds of death was detected (OR, 0.83; 95% CI, 0.70 to 0.98; p=0.03) when compared with untreated controls.

Literature Search Results (1987-2007)

The literature search identified 38 relevant reports representing 31 RCTs as well as 13 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 of more mature data of full publications included in Version 1 of this guideline as well as full publications of abstract data included in Version 1. Publications of regimens no longer in use were excluded from this version of the guideline. New trials were also identified that were published after 2007. In total, this version of the guideline includes 26 unique reports [1-6,8-15,24-35] representing 18 RCTs that reflect the complete evidence base considered relevant by the Working Group. In addition, 12 meta-analyses/pooled analyses reported in 13 papers [7,23,36-46] were included. One other new meta-analysis was identified. It was excluded as a number of treatment modalities were pooled and it was unclear what the contribution of systemic chemotherapy alone was. A summary of all included studies in this update (i.e., Version 2) is provided in Table 1. For the abbreviations of clinical trial group names, please see Appendix 5, and for details regarding chemotherapy regimens, see Appendix 6.

Table 1. Studies selected for inclusion.

Study type	Number of trials (papers) in category	References (not mutually exclusive)	Summary of results
Randomized Controlled Trials			
Fluoropyrimidine-based systemic CT vs. observation	10 (10)	[1-4,9,10,24-27]	Appendix 7
Oral fluoropyrimidines vs. IV 5-FU	5 (8)	[11-15,29,31,34]	Table 5
Fluoropyrimidines + oxaliplatin vs. fluoropyrimidines	3 (7)	[5,6,8,30,32,33,35]	Table 6
Fluoropyrimidine + oxaliplatin in stage II vs. stage III	1 (1)	[5]	Table 7
Effect of chemotherapy in those aged ≤70 vs. >70 years old	4 (4)	[6,11,28,33]	Table 8
Meta-analyses of Randomized Controlled Trials			
Fluoropyrimidine-based CT vs. observation	11 (12)	[23,36-46]	Appendix 7
MSI status of stage II patients	1 (1)	[7]	Table 9

Notes: 5-FU, 5-fluorouracil; CT, chemotherapy; IV, intravenous; MSI, microsatellite instable; vs, versus.

Biologic Agents in the Adjuvant Setting

Evidence for biologic agents were identified but failed to show benefit and will not be discussed further. One such regimen was fluoropyrimidine plus bevacizumab (Bev), which was evaluated in the AVANT [12] and the NSABP C-08 [47] trials. Both of these trials failed to demonstrate a DFS benefit in stage II [47] or stage III [12,47]. Moreover, the NSABP C-08 [47] trial failed to demonstrate an OS benefit in either the stage II or III setting.

The other biologic regimen studied was fluoropyrimidine plus cetuximab, which was evaluated in Alberts et al. [48] and PETACC8 [49,50]. Both of these trials, which only included stage III patients, failed to demonstrate a DFS benefit in either *KRAS* wild type or mutant *KRAS* patients. Furthermore, Alberts et al. [48] failed to demonstrate an OS benefit in *KRAS* wild type or mutant *KRAS* patients. PETACC8 [49,50] did not report OS results.

Study Design and Quality

Risk of Bias (http://handbook.cochrane.org/ - Part 2, Section 8.5) was assessed for each of the 18 unique RCTs included in this guidance document. For trials with multiple published reports, all reports were searched for the relevant information. Although none of the trials had a high risk of bias with respect to selection bias (i.e., random sequence generation and allocation concealment), many studies scored 'unclear' (Table 2). This occurred when a trial report did not include enough detail about their randomization processes to make an informed judgement. With respect to performance bias (blinding of participants *and* personnel), most studies were rated as 'unclear' owing to lack of reporting. SIx studies [5,8,10-12,13,32-35] scored as high risk of bias as they were reported as open label trials. All but three studies [4,10,15] did not report on blinding of outcome assessment (detection bias). Almost all studies had low risk of bias with respect to attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other sources of bias (Table 2).

Table 2: Risk of bias of included randomized controlled trials

Trial	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Windle 1987 [27]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Gray 1987 [1] (ANZBCT 8201)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low
Francini 1994 [9]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
O'Connell 1997 [26]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Zaniboni 1998 [3] (GIVIO-SITAC 01)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
McDermott 2003 [25]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Gray 2007 [2] (QUASAR)	Low	Low	Unclear	Unclear	Low	Low	Low
Schippinger 2007 [4]	Low	Low	Unclear	Low	Low	Low	Low
Kato 2002 [24]	Low	Low	Unclear	Unclear	Low	Low	Low
Hamaguchi 2011 [10]	Low	Low	High	Low	Low	Low	Low
X-ACT (Twelves 2012/2005, Scheithouer 2003) [11,31,34]	Unclear	Low	High	Unclear	Low	Low	Low
NSABP C-06 (Lembersky 2006/ Kopec 2007) [14,29]	Low	Unclear	Unclear	Unclear	Low	Low	Low
JCOG0205 Shimada 2014 [13]	Low	Unclear	High	Unclear	Low	Low	Low
AVANT deGramont 2012 [12]	Low	Unclear	High	Unclear	Low	Low	Low
Pectasides 2015 [15]	Unclear	Unclear	Unclear	Unclear	High	Low	Low
MOSAIC (Andre 2009/Andre 2004/Tournigand 2012) [5,33,35]	Low	Low	High	Unclear	Low	Low	Low
NSABP C-07 (Yothers 2011/Kuebler 2007) [6,30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
XELOXA (Schmoll 2012/2007) [8,32]	Unclear	Low	High	Unclear	Low	Low	Low

Other methodological quality characteristics were assessed for each of the 18 unique RCTs. For trials with multiple published reports, all reports were searched for the relevant information (Table 3). Generation of allocation sequence, allocation concealment, and blinding were the same as in the Risk of Bias tool above. Eleven trials reported ITT analyses [1-3,5,8-12,25,26,31-35], two trials did not report this feature [4,27], and five studies did not perform an ITT analysis [6,13-15 ,24,29,30]. Withdrawals were described in all but one study [3]. Nine studies had industry funding [2,3,5,8,10-12,14,24,29,31-35], six studies did not have industry funding [1,6,9,13,15,26,30,] and three studies did not report on the source of their study funding [4,25,27]. Statistical power and target sample size calculations were reported in all but four of the RCTs [1,25-27]. Five studies did not report on loss to follow-up [3,5,10,12,24,33,35]. Baseline characteristics were reported on and balanced in all but the one study [1] that did not report on this feature. Only four of the RCTs were terminated early; one for loss of funding [9], one for benefit [26], and two for slow accrual [4,15] (Table 3).

Table 3. Methodological quality characteristics of identified randomized controlled trials.

Trial	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Windle 1987 [27]	NR	NR	NR	NR	Yes	NR	NR	Yes	Yes	No
Gray 1987 [1] (ANZBCT 8201)	NR	NR	NR	Yes	Yes	No	NR	Yes	NR	No
Francini 1994 [9]	NR	NR	NR	Yes	Yes	No	Stage 2 - 80% power to detect a difference in recurrence rate of 0.17, α=0.05 with 80 patients per arm (160 total). Actual accrual 119 pts. Stage 3 – 80% power to detect a difference in recurrence rate of 0.22, α=0.05 with 64 per arm (128 total). Actual accrual 115.	Yes	Yes	Yes, for loss of funding
O'Connell 1997 [26]	NR	NR	NR	Yes	Yes	No	NR	Yes	Yes	Yes, for benefit
Zaniboni 1998 [3] (GIVIO-SITAC 01)	NR	NR	NR	Yes	No	Yes	80% power to detect a 30% relative mortality reduction, two-sided, α=0.05.	NR	Yes	No
McDermott 2003 [25]	NR	NR	NR	Yes	Yes	NR	Reported as "under-powered" but no calculations provided.	No	Yes	No
Gray 2007 [2] QUASAR	Yes	Yes	NR	Yes	Yes	Yes	80% power to detect a 5% improvement in survival with at least 2500 pts and α<0.05. Actual accrual 3239.	Yes	Yes	No
Schippinger 2007 [4]	Yes	Yes	NR	NR	Yes	NR	85% power to detect a difference in OS of 10% between the two study arms, two-sided, α=0.05 with 318 pts per arm (636 total). Actual accrual 535	Yes	Yes	Yes, for slow accrual
Kato 2002 [24]	Yes	Yes	NR	No	Yes	Yes	To detect a 12% increase in 5-year survival rate (from 70% in control arm to 82% in UFT arm) with 140 pts per arm (280 total), α=0.05; β=0.2. Actual accrual 320.	NR	Yes	No
Hamaguchi 2011 [10]	Yes	Yes	No	Yes	Yes	Yes	80% power to detect a HR of 0.67 (i.e., hazard decreased with UFT), one-sided, α=0.05, β=0.2 with 500 pts. Actual accrual 334.	NR	Yes	No
X-ACT (Twelves 2012/2005, Scheithauer 2003) [11,31,34]	NR	Yes	No	Yes	Yes	Yes	80% power to detect non-inferiority with respect to DFS assuming 15% of pts excluded from the per-protocol analysis, 1956 pts and a non-inferiority boundary of 1.25, α=0.025 and assuming 3-yr DFS of 70%. Actual accrual 1987.	Yes	Yes	No
NSABP C-06 (Lembersky 2006/ Kopec 2007) [14,29]	Yes	NR	NR	Yes	Yes	Yes	No more than a 15% chance of erroneously concluding equivalence of the two regimens if the 5-year survival difference decreased from 0.74 for FU+LV to 0.69 for UFT+LV.	Yes	Yes	No

Trial	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
JCOG0205 Shimada 2014 [13]	Yes	NR	No	No	Yes	No	78% power to detect non-inferiority with respect to DFS with 1100 pts and a non-inferiority boundary of 1.27, one-sided, α=0.05. Actual accrual 1101.	Yes	Yes	No
AVANT deGramont 2012 [12]	Yes	NR	No	Yes	Yes	Yes	80% power to detect a 23% reduction in the HR for DFS, two-sided log-rank test, α=0.025 and 2880 pts. Actual accrual 3451.	NR	Yes	No
Pectasides 2015 [15]	NR	NR	Nr	No	Yes	No	80% power to detect a 5% difference in baseline 3-year DFS of 78.2% with 824 pts, two-sided, α=0.05, 3% withdrawal rate. Actual accrual 441.	Yes	Yes	Yes, for slow accrual
MOSAIC (Andre 2009/Andre 2004/Tournigand 2012) [5,33,35]	Yes	Yes	No	Yes	Yes	Yes	90% power to detect a 6% difference in 3-year DFS (73% in control arm and 79% in FOLFOX4 arm), two-sided, α=0.05 with 2200 pts. Actual accrual 2246.	NR	Yes	No
NSABP C-07 (Yothers 2011/ Kuebler 2007) [6,30]	NR	NR	NR	No	Yes	No	89% power to detect a 5% improvement in 5-year OS with 2472 pts. Actual accrual 2492.	Yes	Yes	No
XELOXA (Schmoll 2007 Schmoll 2012) [8,32]	NR	Yes	No	Yes	Yes	Yes	80% power to detect a 6% difference in DFS (62% in the control arm and 68% in the XELOX arm), two-sided, α=0.05 with 1850 patients. Actual accrual 1886.	No	Yes	No

Notes: 5-FU, 5-fluorouracil; DFS, disease-free survival; FOLFOX4, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; ITT, intention to treat; LV, leucovorin; NR, not reported; OS, overall survival; pts, patients; UFT, uracil-tegafur; XELOX, capecitabine/oxaliplatin.

Included SRs (with or without meta-analyses) were evaluated for quality using the AMSTAR tool [22] (Table 4). All 12 of the included SRs provided an 'a priori' design and all 12 SRs used appropriate methods to combine the findings of the individual studies included in them. None of the SRs assessed the likelihood of publication bias or did a comprehensive literature search. Only two SRs [38,42] reported duplicate study selection and data extraction. Only one SR used the status of publication as an inclusion criterion [42], provided a list of included *and* excluded studies [23], assessed the quality of the included studies [38], or used the quality of the included studies in formulating their conclusions [38]. Eight SRs provided information on the characteristics of the studies [23,36,37,41-46] and only five made conflict of interest statements [7,39,40,43,44] (Table 4).

Table 4: Evaluation of included systematic reviews (with or without meta-analyses) using AMSTAR.

ITEM	Intravenous chemotherapy versus observation									Oral chemotherapy versus observation		MSI versus MSS
	Buyse 1988 [23]	IMPACT1 1995.2001 [36,41]	IMPACT 2 1999 [37]	Zalcberg 1996 [46]	Dube 1997 [38]	Sargent 2001 [45]	Gill 2004 [39]	Glimelius 2005 [40]	Sargent 2009 [44]	Sakamoto 1999 [42]	Sakamoto 2004 [43]	Sargent 2010 [7]
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	N	N	N	N	Y	N	N	N	N	Y	N	N
3. Was a comprehensive literature search performed?	N	N	N	N	N	N	N	N	N	N	N	N
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	N	N	N	N	N	N	N	N	N	Y	N	N
5. Was a list of studies (included and excluded) provided?	Y	N	N	N	N	N	N	N	N	N	N	N
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	N
7. Was the scientific quality of the included studies assessed and documented?	N	N	N	N	Y	N	N	N	N	N	N	N
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	N	N	N	N	Y	N	N	N	N	N	N	N
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the likelihood of publication bias assessed?	N	N	N	N	N	N	N	N	N	N	N	N
11. Was the conflict of interest stated?	N	N	N	N	N	N	Y	Y	Y	N	Y	Y

Notes: MSI, microsatellite instable; MSS, microsatellite stable.

Outcomes

Question 1: What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy versus observation on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

Randomized Controlled Trials

As there is a large amount of these data and they were presented in the original version of this guideline, the results of RCT data for this comparison are described in more detail in Appendix 7 (Table 10). In total, 10 trials [1-4,9,10,24-27] have compared the use of various IV and oral fluoropyrimidine-based chemotherapy regimens with observation alone in patients with colon or colorectal cancer. Many trials included patients with both stage II and III colon cancer, and several also included patients with rectal cancer. The convention has been that high-risk stage II patients with a risk of recurrence approximating that of stage III patients are also likely to obtain similar benefit from chemotherapy. These trials, however, have not generally reported outcomes separately for high-risk and low-risk stage II patients, making this assessment difficult (Appendix 7, Table 10).

Meta-analyses of Randomized Controlled Trials

Meta-analyses of trials comparing adjuvant chemotherapy with observation for colorectal cancer (Appendix 7, Table 11) generally demonstrate superior DFS and OS for the chemotherapy arms (DFS HRs: 0.65 to 0.87; OS HRs: 0.74 to 0.86), particularly for stage III patients. Although HRs also favoured chemotherapy for stage II patients, these were not statistically significant [36,40,41] except for DFS in Gill et al. [39] and OS in Sargent et al. [44]. These pooled analyses did not separate high-risk versus low-risk patients; therefore, these studies alone are insufficient to base recommendations for the high-risk stage II population.

Question 2: What is the impact of adjuvant IV 5-FU versus oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

Oral Fluoropyrimidines versus Intravenous 5-FU

Three fully published RCTS sought to demonstrate non-inferiority of oral versus IV fluoropyrimidines [11,13,14], with the goal of having a less toxic or more convenient mode of delivery. The X-ACT trial compared oral capecitabine with intravenous bolus 5-FU/LV (Mayo Clinic regimen) [11], the NSABP C-06 [14] trial compared oral uracil-tegafur (UFT) plus LV with IV 5-FU/LV, and JCOG0205 [13] compared oral UFT/LV with intravenous 5-FU plus levofolinate (I-LV) (Table 5). The X-ACT and JCOG0205 trials included only patients with resected stage III tumours while the NSABP C-06 included patients with either stage II or III tumours. The X-ACT and NSABP C-06 trials reported pharmaceutical sponsorship. X-ACT [11] and JGOC0205 [13] were not blinded. Blinding information is not reported in NSABP C-06 [14]. The method of patient randomization was not adequately described for any of these non-inferiority trials. The NSABP C-06 study stratified patients according to the number of involved lymph nodes, the X-ACT study stratified patients according to treatment centre, and the JOCG0205 trial stratified patients by tumour location, number of positive lymph nodes and institution. All studies reported the statistical calculations used to determine trial power and target sample sizes.

The AVANT trial [12] was a three-arm superiority trial of FOLFOX4 versus FOLFOX4 plus Bev versus XELOX plus Bev. Although not the focus of this trial, a comparison of the latter two arms was germane to the question regarding oral versus IV fluoropyrimidines. This study

reported pharmaceutical sponsorship. It was not blinded or placebo controlled. The method of patient randomization was adequately described. Patients were stratified according to geographic region and disease stage. Statistical calculations used to determine trial power and target sample size were reported.

The Pectasides trial [15] was a two-arm superiority trial of CAPOX versus mFOLFOX6 in patients with resected high-risk stage II or stage III tumours. This trial did not report pharmaceutical sponsorship. Randomization was not adequately described and blinding was not reported. Patients were stratified by stage. Power and sample size calculations were provided. This trial was terminated early owing to slow accrual.

Disease-free Survival

All three non-inferiority studies [11,13,14] demonstrated equivalent efficacy with respect to DFS for oral fluoropyrimidines compared with IV 5-FU/LV (Table 5). The X-ACT [11] study showed capecitabine to be at least as effective as 5-FU/LV for stage III patients (non-inferiority $p<0.0001$). Although these results favoured capecitabine, the observed difference between groups was statistically non-significant in the superiority analysis as well (HR, 0.88; 95% CI, 0.77 to 1.01; $p=0.068$). The JCOG0205 trial [13] demonstrated equivalence of UFT/LV to 5-FU/l-LV with respect to DFS (HR, 1.02; 95% CI, 0.84 to 1.23; $p=0.0236$). Similarly, the NSABP C-06 [14] study concluded that the UFT/LV and 5-FU/LV were equivalent for DFS (HR, 1.004; 95% CI, 0.847 to 1.19; $p=0.96$). Results for the DFS outcome were not reported separately for stage II and III patients in this study. In the AVANT trial [12], three-year DFS was 73% in the FOLFOX4/Bev arm and 75% in the XELOX/Bev arm. No statistical comparison was provided. In the Pectasides [15] trial, three-year DFS was 79.5% in the CAPOX arm and 79.8% in the mFOLFOX6 arm (HR, 0.91; 95% CI, 0.58-1.44, $p=0.0784$) (Table 5).

Overall Survival

Two of the non-inferiority studies comparing oral regimens with intravenous 5-FU/LV demonstrated no significant difference in OS between treatment groups [11,14]. In the X-ACT study of stage III patients, the mortality HR was 0.86 (95% CI, 0.74 to 1.01) favouring capecitabine (non-inferiority $p<0.000116$); however, this difference was not significant in the superiority analysis ($p=0.06$) [11]. The NSABP C-06 study [14] reported a mortality HR of 1.014 favouring 5-FU/LV for the overall analysis of stage II and III patients, but this difference was also not significant ($p=0.90$). Although five-year OS data were reported separately for stage II and III patients, no statistical comparisons were performed. In the JCOG0205 trial [13], five-year OS was 87.5% and 88.4% in the UFT/LV and 5-FU/l-LV arms, respectively. The HR for survival was 1.05 (95% CI, 0.77-1.44). No statistical comparison was reported. In the AVANT superiority trial [12], five-year OS was 81% in the FOLFOX4/Bev arm and 82% in the XELOX/Bev arm. No p-value was reported. The Pectasides trial [15] reported no significant difference in three-year OS between the CAPOX and mFOLFOX6 arms (86.9% and 87.2% respectively; HR, 1.05; 95% CI, 0.68-1.60; $p=0.844$) (Table 5).

Adverse Effects

A safety analysis of the X-ACT study was performed 19 months after the enrolment of the last patient, and the results were published separately from the efficacy results [31]. Patients in the capecitabine group experienced significantly less grade 3/4 stomatitis (2% versus 14%), grade 3/4 neutropenia requiring intervention (0.6% versus 5%), and febrile neutropenia/sepsis (0.3% versus 3%) than did those in the 5-FU/LV group. In addition, patients who received capecitabine experienced significantly less diarrhea (46% versus 64%), nausea/vomiting (36% versus 51%), and alopecia (6% versus 22%) of all grades. The only treatment-related toxicity that occurred more frequently in patients who received

capecitabine compared with those who received 5-FU/LV was hand-foot syndrome (62% versus 10% all grades, 18% versus 0.6% grade 3; p<0.001). Dose reduction was similar in both treatment groups (42% in patients who received capecitabine and 44% in patients who received 5-FU/LV), but median time to first dose reduction was longer in the capecitabine group (78 versus 41 days).

In the NSABP C-06 study, toxicities were similar for patients who received UFT/LV and 5-FU/LV [14]. In both treatment arms, 38% of patients experienced a grade 3 or higher non-hematological toxicity as their worst toxicity, and 20% experienced a grade 4 or higher non-hematological toxicity as their worst toxicity. Diarrhea was the most frequent severe toxicity in both groups (29%).

In the JCOG0205 study [13], grade 3 or 4 neutropenia occurred in 8.4% of 5-FU/I-LV patients and 1.5% of UFT/LV patients. No p-value was provided. In addition, there were similar rates of diarrhea (9.6% versus 8.5%) and anorexia (4.0% versus 3.7%) in the 5-FU/I-LV and UFT/LV arms although no p-values were reported.

In the AVANT trial [12], grade 3 to 5 toxicities were experienced by 76% of the patients in the FOLFOX4/Bev arm and 65% of patients in the XELOX/Bev arm. Grade 3 and 4 toxicity rates were similar in the two arms with the exception of neutropenia, which occurred more in the FOLFOX4/Bev arm (37% versus 6%) and hand-foot syndrome, which occurred more in the XELOX/Bev arm (8% versus 1%). No statistical comparisons were reported.

In the Pectasides study [15], Grade 3 and 4 neutropenia occurred significantly more in the mFOLFOX6 arm compared (26.9% vs. 8.1%, p<0.0002) whereas Grade 3 and 4 vomiting occurred significantly more in the CAPOX arm (1.57% vs. 0%, p=0.012).

Quality of Life

In the X-ACT study, quality of life was measured using the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer at baseline and at the beginning of every treatment cycle [34]. The scores remained relatively constant over time in both the capecitabine group and the 5-FU/LV group, but both increased slightly at week 25 of treatment. In the NSABP C-06 study, quality of life results were reported in a separate publication [29]. Health-related quality of life (HRQL) was measured at baseline, at week 15/16, and at one year. No difference in HRQL was reported between the UFT/LV group and the 5-FU/LV group. A convenience of care scale and symptoms scales were administered at baseline, at the beginning of each treatment cycle, and at one year. Patients who received UFT/LV scored significantly higher on the convenience of care scale and on two symptoms scales. Patients who received 5-FU/LV scored marginally higher on the Short Form-36 Vitality Scale. Overall, HRQL scores improved slightly over time in both treatment arms. JCOG0205 [13], AVANT [12], and Pectasides [15] did not report quality of life data.

Table 5. Randomized controlled trials of oral fluoropyrimidines versus intravenous 5-FU.

Trial, year (reference)	Type of trial	Treatment allocation	Months on therapy	Number of patients evaluated		Median follow-up (years)	All trial patients		Stage II patients		Stage III patients	
				Stage II	Stage III		DFS	OS	DFS	OS	DFS	OS
Twelves, 2012 [11] X-ACT	Non-inferiority	Capecitabine IV 5-FU/LV (Mayo regimen)	5.5 5.5	- -	1004 983	6.9	- -	- -	- -	- -	5-year 60.8% 56.7% HR 0.88 (95% CI 0.77-1.01) p=0.068*	5-year 71.4% 68.4% HR 0.86 (95% CI 0.74-1.01) p=0.06*
Lembersky, 2006 [14] NSABP C-06	Non-inferiority	Oral UFT + LV IV 5-FU/LV	5.8 5.5	365 357	416 413	5.2	5-year 67.0% 68.2% HR 1.004 (95% CI 0.85-1.19) p=0.96	5-year 78.5% 78.7% HR 1.014 (95% CI 0.83-1.25) p=0.90	NR	5-year 88.4% 87.0% p=NR	NR	5-year 69.6% 71.5% p=NR
Shimada, 2014 [13] JCOG0205	Non-inferiority	Oral UFT + LV IV 5-FU/I-LV	5.8 5.5	- -	546 546	6.0	- -	- -	- -	- -	5-year 73.6% 74.3% HR 1.02 (95% CI 0.84-1.23) p=0.0236	5-year 87.5% 88.4% HR 1.05 (95% CI 0.77-1.44) p=NR
de Gramont, 2012 [12] AVANT	Superiority	FOLFOX4 + Bev XELOX + Bev	11.1 11.1	194 187	960 952	>4	NR	NR	NR	NR	3-year 73% 75% p=NR	5-year 81% 82% p=NR
Pectasides 2015 [15]	Superiority	CAPOX mFOLFOX6	5.5 5.5	211 197		6.2	3-year 79.5% 79.8% HR 0.91 (95% CI 0.58-1.44) p=0.784	3-year 86.9% 87.2% HR 1.05 (95% CI 0.68-1.60) p=0.844				

Notes: 5-FU, 5-fluorouracil; Bev, bevacizumab; CI, confidence interval; DFS, disease-free survival; FOLFOX4, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; I-LV, levofolinate; LV, leucovorin; NR, not reported; OS, overall survival; UFT, uracil-tegafur; XELOX, capecitabine/oxaliplatin.
*****p-values are for superiority tests. Values for non-inferiority tests are p<0.0001 for DFS and p<0.000116 for OS.

Question 3a: What is the impact of adjuvant fluoropyrimidines versus fluoropyrimidines plus oxaliplatin on DFS and OS in patients with:

i) **stage II or III colon cancer who have undergone complete resection with curative intent?**
ii) **stage II colon cancer who have undergone complete resection with curative intent?**
iii) **stage III colon cancer who have undergone complete resection with curative intent?**

Fluoropyrimidines plus Oxaliplatin versus Fluoropyrimidines Alone

Three fully published RCTs were obtained that compared 5-FU plus oxaliplatin with 5-FU alone for the adjuvant treatment of colon carcinoma: the MOSAIC [5], NSABP C-07 [6], and XELOXA studies [8] (Table 6). Toxicity data are available for all three trials [6,30,32,35]. Two of the RCTs administered oxaliplatin with intravenous 5-FU/LV, one using the FOLFOX4 regimen [5] and one using the FLOX regimen [6]. FLOX, while containing oxaliplatin, is a different regimen and is only used in very limited circumstances. One of the RCTs compared capecitabine plus oxaliplatin (XELOX) with bolus 5-FU/LV [8] (see Appendix 6 for regimen details). The MOSAIC [5] and the NSABP C-07 [6] trials included patients with stage II and III disease, while the XELOXA study [8] included only patients with stage III disease. Two of the RCTs reported pharmaceutical sponsorship [5,8]. Two of the studies were not blinded [5,8] and one did not report on blinding [6]. The method of patient randomization was adequately described in MOSAIC [5] and inadequately described in NSABP C-07 [6] and XELOXA [8].

Disease-Free Survival

In overall analyses of patients with resected stage II and III colon cancer, both the MOSAIC study [5] and the NSABP C-07 study [6] demonstrated a significant benefit in DFS for fluoropyrimidine plus oxaliplatin compared with 5-FU/LV regimens alone (Table 6). The MOSAIC study performed separate analyses of stage II and III patients and demonstrated a significant benefit for the addition of oxaliplatin in stage III patients (HR, 0.78; 95% CI, 0.65 to 0.93; p=0.005) but not for stage II patients (HR 0.84; 95% CI, 0.62 to 1.14; p=0.258). A subgroup analysis of low-risk and high-risk stage II patients was also reported in a separate publication [33]. In this analysis, patients were considered high-risk stage II if they had at least one of the following characteristics: T4, tumour perforation, bowel obstruction, poorly differentiated tumour, venous invasion, or fewer than 10 lymph nodes examined. There was no significant benefit in DFS for fluoropyrimidine plus oxaliplatin compared with 5-FU/LV alone. Specifically, in the high-risk patients, five-year DFS was 82.3% versus 74.6%, favouring FOLFOX4 with a non-significant overall DFS (HR, 0.72; 95% CI, 0.51 to 1.02; p=0.063) [33]. It should be noted that the MOSAIC trial was powered for DFS in the whole population (i.e., stage II and III). The authors warn that the trial is underpowered for subgroup analyses and, therefore, should be considered to be exploratory only. The NSABP C-07 trial [6] also performed separate analysis of stage II and III patients and demonstrated a significant benefit for the addition of oxaliplatin in stage III patients (HR, 0.78; 95% CI, 0.68 to 0.90; p<0.001) but not for stage II patients (HR, 0.94; 95% CI, 0.70 to 1.26; p=0.67). XELOXA [8] only included stage III patients and reported a significant benefit for DFS for the XELOX regimen compared with the bolus 5-FU/LV regimen (HR, 0.80; 95% CI, 0.69 to 0.93; p=0.0038) (Table 6).

Overall Survival

After more than six years of follow-up, the MOSAIC trial reported improved survival in the oxaliplatin group (HR, 0.84; 95% CI, 0.71 to 1.00; p=0.046) [5]. Separate analyses according to disease stage indicated a significant survival benefit for oxaliplatin compared with 5-FU/LV alone in stage III patients (HR, 0.80; 95% CI, 0.65 to 0.97; p=0.023) but no difference between groups in stage II patients (HR, 1.00; 95% CI, 0.70 to 1.41; p=0.986). The MOSAIC subgroup analysis of low-risk and high-risk stage II patients demonstrated no significant benefit in OS for fluoropyrimidine plus oxaliplatin compared with 5-FU/LV alone. Six-year OS was 85.0% versus 83.3% favouring FOLFOX4 with an overall non-significant OS (HR, 0.91; 95% CI, 0.61 to 1.36; p=0.48) [33]. The results of the NSABP C-07 [6] were different than MOSAIC in that improved survival was not demonstrated in the overall group (HR, 0.88; 95% CI, 0.88 to 1.02; p=0.08). Separate analysis by stage did not demonstrate a significant benefit for oxaliplatin compared with 5-FU/LV alone in either stage III patients (HR, 0.85; 95% CI, 0.72 to 1.00; p=0.052) or stage II patients (HR, 1.04; 95% CI, 0.72 to 1.50; p=0.84). XELOXA [8] only included stage III patients in the trial and reported a significant benefit for OS for the XELOX regimen compared with bolus 5-FU/LV (HR, 0.83; 95% CI, 0.70 to 0.99; p=0.0367) (Table 6).

Adverse Effects

Adverse effects for the MOSAIC trial are reported in a separate paper [35]. The MOSAIC study reported significantly higher grade 3 or 4 paresthesia, neutropenia, thrombocytopenia, nausea, diarrhea, vomiting, allergic reaction, and neutropenia with fever or infection in patients who received 5-FU/LV plus oxaliplatin compared with patients who received 5-FU/LV alone. During treatment, 92.1% of patients who received oxaliplatin had peripheral neuropathy but only 12.4% experienced grade 3 neuropathy [35]. After four years, 11.9% of evaluable patients continued to experience grade 1 peripheral sensory neuropathy, 2.8% grade 2, and 0.7% grade 3 [5].

The NSABP C-07 study reported grade 2 or greater neurosensory toxicity in 30.4% of patients who received oxaliplatin in the FLOX regimen, compared with 3.6% of patients who received 5-FU/LV alone [6]. Grade 3 or greater toxicities in the 5-FU/LV versus FLOX arms were as follows: diarrhea (32.4% versus 38.1%), nausea (11.0% versus 15.6%), and vomiting (7.9% versus 12.1%). No statistical comparisons were provided. NSABP C-07 also reported that 4.3% of all patients developed severe enteropathy. Of these, 64.6% occurred in patients in the FLOX arm and 35.4% occurred in patients in the 5-FU/LV arm (p<0.01) [30].

A final safety analysis of the XELOXA study reported 55% grade 3 or 4 adverse events in the XELOX group compared with 47% in the bolus 5-FU/LV group. Patients in the XELOX group experienced less neutropenia, febrile neutropenia, and stomatitis but more thrombocytopenia, neurosensory toxicity, and hand-foot syndrome than did patients in the bolus 5-FU/LV group. Sixty-day all-cause mortality (1% in each group) and treatment-related death within 28 days from last dose (0.6% in each group) were similar between treatment groups [32].

Quality of Life

None of the three RCTs comparing 5-FU plus oxaliplatin with 5-FU alone have reported data for quality of life outcomes [5,6,8].

Table 6. Randomized controlled trials of fluoropyrimidines plus oxaliplatin versus fluoropyrimidines alone.

Trial, year (reference)	Treatment allocation	Months on therapy	Number of patients evaluated		Median follow-up (years)	All trial patients		Stage II patients		Stage III patients	
			Stage II	Stage III		DFS	OS	DFS	OS	DFS	OS
Andre, 2009 MOSAIC [5]	LV5FU2 FOLFOX4	5.5	448 451	675 672	>6.1	5-year 67.4% 73.3% HR, 0.80 (95% CI 0.68-0.93) p=0.003	6-year 76.0% 78.5% HR, 0.84 (95% CI 0.71-1.00) p=0.046	5-year 79.9% 83.7% HR, 0.84 (95% CI 0.62-1.14) p=0.258	6-year 86.8% 86.9% HR, 1.00 (95% CI 0.70-1.41) p=0.986	5-year 58.9% 66.4% HR, 0.78 (95% CI 0.65-0.93) p=0.005	6-year 68.7% 72.9% HR, 0.80 (95% CI 0.65-0.97) p=0.023
Tournigand 2012 [33] (for low-/ high-risk stage II)			**Low risk** =330 **High risk** = 569					**Low-risk pts** 89.3% 86.0% HR, 1.36 (95% CI 0.76-2.45, p=0.305 **High-risk pts** 74.6% 82.3% HR, 0.72 (95% CI 0.51-1.02, p=0.063	**Low-risk pts** 93.0% 90.2% HR, 1.36 (95% CI 0.67-2.78, p=0.399 **High-risk pts** 83.3% 85.0% HR, 0.91 (95% CI 0.61-1.36, p=0.48		
Yothers, 2011 NSABP C-07 [6]	5-FU/LV FLOX	6	1209 total 1200 total		8	5-year 64.2% 69.4% HR, 0.82 (95% CI 0.72-0.93) p=0.002	5-year 78.4% 80.2% HR, 0.88 (95% CI 0.88-1.02) p=0.08	HR, 0.94 (95% CI 0.70-1.26) p=0.67	HR, 1.04 (95% CI 0.72-1.50) p=0.84	HR, 0.78 (95% CI 0.68-0.90) p<0.001	5-year 73.8% 76.5% HR, 0.85 (95% CI 0.72-1.00) p=0.052
Schmoll, 2012 XELOXA [8] *abstract*	Bolus 5-FU/LV XELOX	5.5 or 7.4 5.5	- -	942 944	>6.2	- -	- -	NR	NR	7-year 56% 63% HR, 0.80 (95% CI 0.69-0.93) p=0.0038	7-year 67% 73% HR, 0.83(95% CI 0.70-0.99) p=0.0367

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; DFS, disease-free survival; FLOX, 5-FU/LV/oxaliplatin; FOLFOX4, 5-FU/leucovorin/oxaliplatin; HR, hazard ratio; LV5FU2, leucovorin/5-FU; LV, leucovorin; NR, not reported; pts, patients; OS, overall survival; XELOX, capecitabine/oxaliplatin.

Question 3b: What is the impact of stage (II or III) of colon cancer on DFS and OS with the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in patients who have undergone complete resection with curative intent?

Fluoropyrimidines plus Oxaliplatin in Stage II versus Stage III

One fully published RCT was obtained that contained data on fluoropyrimidine plus oxaliplatin (in the form of FOLFOX4) parsed by stage [5]. The purpose of MOSAIC was to compare 5-FU plus oxaliplatin with 5-FU alone for the adjuvant treatment of colon carcinoma but it was possible to abstract data for outcomes related to stage II and III in the FOLFOX4 arm.

Disease-Free Survival

Five-year DFS in the MOSAIC [5] FOLFOX4 arm was 83.7% in stage II patients and 66.4% in stage III patients (Table 7). Since the purpose of MOSAIC was not to compare FOLFOX4 in stage II and II patients, no statistical analysis of these data was available.

Overall Survival

Six-year OS in the MOSAIC [5] FOLFOX4 arm was 86.9% in stage II patients and 72.9% in stage III patients (Table 7). Since the purpose of MOSAIC was not to compare FOLFOX4 in stage II and II patients, no statistical analysis of these data was available.

Adverse Effects

Adverse effects for the MOSAIC trial are reported in a separate paper [34] but toxicities were not reported by stage for either arm of the study.

Quality of Life

Quality of life data were not reported.

Table 7. Randomized controlled trials of fluoropyrimidines plus oxaliplatin in stage II versus stage III colon cancer patients.

Trial, year (reference)	Treatment allocation	Months on therapy	Number of patients evaluated	Median follow-up (years)	DFS	OS
Andre, 2009 MOSAIC [5]	Stage II Stage III	5.5	451 672	>6.1	5-year 83.7% 66.4% p=NR	6-year 86.9% 72.9% p=NR

Notes: DFS, disease-free survival; NR, not reported; OS, overall survival.

Question 4a: What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

Fluoropyrimidines plus Oxaliplatin in those ≤70 Years of Age versus >70 Years of Age

Three RCTs were obtained that compared a fluoropyrimidine plus oxaliplatin regimen with a fluoropyrimidine regimen alone for the adjuvant treatment of colon carcinoma in patients ≤70 years, and >70 years of age [6,28,33] (Table 8). These three trials have been described previously for Question 3 of this guidance document.

Disease-Free Survival

MOSAIC and NSABP C-07 [6,33] both reported a significant benefit in patients less than 70 years of age for the addition of oxaliplatin to a fluoropyrimidine regimen compared with a fluoropyrimidine regimen alone (HR, 0.78; 95% CI, 0.66 to 0.92; p=0.003 and HR, 0.76; 95% CI, 0.66 to 0.88; p<0.001, respectively). Although a p-value was not provided in XELOXA, there is likely a significant benefit for the addition of oxaliplatin in this trial as well (HR, 0.79; 95% CI, 0.66 to 0.94) given the HR and p-value seen for DFS in all patients [28]. There was no benefit seen in patients older than 70 years of age in any of the three trials (Table 8).

Overall Survival

MOSAIC and NSABP C-07 [6,33] both reported a significant benefit in patients less than 70 years old for the addition of oxaliplatin to a fluoropyrimidine regimen compared with a fluoropyrimidine regimen alone (HR, 0.80; 95% CI, 0.66 to 0.97; p=0.02 and HR, 0.80; 95% CI, 0.68 to 0.95; p=0.013, respectively). XELOXA does not demonstrate a benefit (HR, 0.86; 95% CI, 0.69 to 1.08) [28]. There was no benefit seen in patients older than 70 years of age in any of the three trials (Table 8).

Adverse Effects

MOSAIC [33] reported that were significantly more serious adverse events in the elderly patients (aged 70 to 75 years) in the FOLFOX4 arm compared with the LV5FU2 arm (p=0.018). NSABP C-07 [6] reported that patients greater than 70 years in both arms of the trial experienced more grade 5 toxicity (death) and greater grade 3 to 5 diarrhea, nausea, and vomiting than those younger than 70 years of age. However, no statistical comparison was reported. XELOXA [28] did not provide information on adverse effects in terms of age group.

Quality of Life

None of the RCTs that compared a fluoropyrimidine plus oxaliplatin regimen with a fluoropyrimidine regimen alone for the adjuvant treatment of colon carcinoma reported quality of life data.

Question 4b: What is the impact of adjuvant fluoropyrimidine monotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

Adjuvant Fluoropyrimidine Monotherapy in those aged ≤70 versus >70 years of age

One RCT (the X-ACT trial) was obtained that compared adjuvant fluoropyrimidine monotherapies in the treatment of colon carcinoma in patients <70 and ≥70 years of age [11] (Table 8). This trial has been described previously for Question 2 of this guidance document.

Disease-Free Survival

X-ACT [11] did not report a significant benefit in patients 40 to 69 or ≥70 years of age for oral capecitabine monotherapy compared with IV 5-FU/LV (HR, 0.87; 95% CI, 0.75 to 1.01; p=NR and HR, 0.97; 95% CI, 0.72 to 1.31; p=NR, respectively) (Table 8).

Overall Survival

The X-ACT trial [11] did not report a significant benefit in patients 40 to 69 or ≥70 years of age for oral capecitabine monotherapy compared with IV 5-FU/LV (HR, 0.87; 95% CI, 0.73 to 1.04; p=NR and HR, 0.91; 95% CI, 0.65 to 1.26; p=NR, respectively) (Table 8).

Adverse Effects

Adverse effects were similar for oral capecitabine and IV 5-FU/LV in patients >70 years of age compared with younger patients [51].

Quality of Life

The X-ACT trial [11] did not report quality of life data.

Table 8. Subgroup analysis based on age of randomized controlled trials of adjuvant chemotherapy in stage II and III colon cancer following complete resection.

Trial, year (reference)	Treatment allocation	Months on therapy	Number of patients evaluated		Median follow-up (years)	All trial patients		Patients ≤70 years old		Patients >70 years old	
			≤70 years	>70 years		DFS	OS	DFS	OS	DFS	OS
ADJUVANT FLUOROPYRIMIDINES + OXALIPLATIN VERSUS FLUOROPYRIMIDINES ALONE											
Tournigand 2012 MOSAIC [33]	LV5FU2 FOLFOX4	5.5	963 968	160 155	>5.2	5-year 67.4% 73.3% HR, 0.80 (95% CI 0.68-0.93) p=0.003	6-year 76.0% 78.5% HR, 0.84 (95% CI 0.71-1.00) p=0.046	5-year NR NR HR, 0.78 (95% CI 0.66-0.92) p=0.003	6-year NR NR HR, 0.80 (95% CI 0.66-0.97) p=0.02	5-year 65.8% 69.1% HR, 0.93 (95% CI 0.64-1.35) p=0.71	6-year 76.1% 75.8% HR, 1.10 (95% CI 0.73-1.65) p=0.661
Yothers, 2011 NSABP C-07 [6]	5-FU/LV FLOX	6	1006 1007	203 193	8	5-year 64.2% 69.4% HR, 0.82 (95% CI 0.72-0.93) p=0.002	5-year 78.4% 80.2% HR, 0.88 (95% CI 0.88-1.02) p=0.08	5-year 64.7% 70.7% HR, 0.76 (95% CI 0.66-0.88) p<0.001	5-year 78.8% 81.8% HR, 0.80 (95% CI 0.68-0.95) p=0.013	5-year 62.0% 62.8% HR, 1.03 (95% CI 0.77-1.36) p=0.87	5-year 76.3% 71.6% HR, 1.18 (95% CI 0.862-1.62) p=0.30
Haller 2010 XELOXA [28] (abstract)	Bolus 5-FU/LV XELOX	5.5 or 7.4 5.5	NR	NR	4.8	3-year 70.9% 66.5% HR, 0.80 (95% CI 0.69-0.93) p=0.0045	5-year NR NR HR, 0.87 (95% CI 0.72-1.05) p=NR	3-year NR NR HR, 0.79 (95% CI 0.66-0.94) p=NR	5-year NR NR HR, 0.86 (95%CI 0.69-1.08) p=NR	3-year NR NR HR, 0.87 (95% CI 0.63-1.18) p=NR	5-year NR NR HR, 0.94 (95%CI 0.66-1.34) p=NR
ADJUVANT FLUOROPYRIMIDINE MONOTHERAPY											
Twelves, 2012 X-ACT [11]	Capecitabine IV 5-FU/LV (Mayo regimen)	5.5	**40-69 years** 1513 total	396 total	6.9	5-year 60.8% 56.7% HR, 0.88 (95% CI 0.77-1.01) p=0.068*	5-year 71.4% 68.4% HR, 0.86 (95% CI 0.74-1.01) p=0.06*	**40-69 years** 5-year 59.4% 54.5% HR, 0.87 (95% CI 0.75-1.01) p=NR	**40-69 years** 5-year 70.9% 68.6% HR, 0.87 (95% CI 0.73-1.04) p=NR	5-year 58.1% 55.8% HR, 0.97 (95% CI 0.72-1.31) p=NR	5-year 68.8% 65.0% HR, 0.91 (95% CI 0.65-1.26) p=NR

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; DFS, disease-free survival; FLOX, 5-FU/LV/oxaliplatin; FOLFOX4, 5-FU/leucovorin/oxaliplatin; IV, intravenous; LV, leucovorin; LV5FU2, leucovorin/5-FU; NR, not reported; pts, patients; OS, overall survival; vs, versus; XELOX, capecitabine/oxaliplatin.
*****p-values are for superiority tests. Values for non-inferiority tests are p<0.0001 for DFS and p<0.000116 for OS.

Question 5: 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?

Microsatellite Instable (MSI) versus Microsatellite Stable (MSS) in Stage II Colon Cancer

One pooled analysis of six RCTs was obtained that contained data on adjuvant fluoropyrimidine chemotherapy (5-FU/LV or 5-FU/levamisole versus surgery alone in patients who were stratified according to DNA mismatch repair (MMR) [7]. There are no data with oxaliplatin. MMR was determined by immunohistochemistry. Patients were classified as either defective MMR/microsatellite instable (MSI) or proficient MMR/microsatellite stable (MSS). These are subgroup analysis only and the number of patients who had MSI was quite small (Table 9).

Disease-Free Survival

In the MSI cohort, DFS was not significantly different in those that had surgery alone compared with those that also had adjuvant chemotherapy (HR, 2.30; 95% CI, 0.84 to 6.24; p=0.09). This was based on a small subgroup of 102 stage II patients only. In the MSS cohort, DFS was also not significantly different in those that had surgery alone compared with those that also had adjuvant chemotherapy (HR, 0.84; 95% CI 0.57 to 1.24; p=0.38) [7] (Table 9).

Overall Survival

In the MSI cohort, OS was significantly worse in those receiving adjuvant chemotherapy compared with those that had surgery alone (HR, 2.95; 95% CI, 1.02 to 8.54; p=0.04) [7] (Table 9). Caution must be exercised in interpreting these results as they are based on a small subgroup of patients and the lower limit of the confidence interval is very close to 1.00. One more death in the surgery arm could change the confidence interval just enough to make this result statistically non-significant.

Table 9. Pooled analysis of randomized controlled trials of adjuvant chemotherapy in stage II colon cancer patients who are MSI versus MSS.

Trial, year (reference)	Treatment allocation	Number of patients evaluated	Median follow-up (years)	DFS	OS
Sargent 2010 [7]	MSI (dMMR) Surgery alone Adjuvant chemotherapy	 55 47	 NR	HR, 2.30; 95% CI 0.84–6.24, p=0.09	HR, 2.95; 95% CI 1.02-8.54, p=0.04
	MSS (pMMR) Surgery alone Adjuvant chemotherapy	 214 214	 NR	HR, 0.84; 95% CI 0.57-1.24, p=0.38	NR

Notes: CI, confidence interval; DFS, disease-free survival; dMMR, defective mismatch repair; HR, hazard ratio; MSI, microsatellite instable; MSS, microsatellite stable; NR, not reported; OS, overall survival; pMMR, proficient mismatch repair.

Ongoing, Unpublished, or Incomplete Studies

Phase III randomized study of adjuvant chemotherapy comprising fluorouracil and irinotecan with or without leucovorin calcium versus no adjuvant therapy in patients with resected stage II adenocarcinoma of the colon	
Protocol ID:	FFCD-EORTC-40012, PETACC-4, NCT00091312
Date last modified:	February 6, 2009
Type of trial:	Randomized, multicentre study
Primary endpoint:	5-year disease-free survival
Accrual:	A total of 1976 patients (988 per treatment arm) will be accrued for this study within 4.5 years.
Sponsorship:	Federation Francophone de Cancerologie Digestive
Status:	Unknown
Phase III randomized study of adjuvant tegafur-uracil versus observation only in patients with curatively resected stage II colorectal cancer	
Protocol ID:	TMDU-BRI-CC-05-01, NCT00392899
Date last modified:	December 17, 2013
Type of trial:	Randomized study
Primary endpoint:	Disease-free survival
Accrual:	2000 patients will be accrued
Sponsorship:	Tokyo Medical and Dental University
Status:	Completed
A study of Xeloda (capecitabine) compared with 5-fluorouracil in combination with low-dose leucovorin in patients who have undergone surgery for colon cancer	
Protocol ID:	NCT00009737
Date last modified:	August 17, 2015
Type of trial:	Randomized study, active control, open-label
Primary endpoint:	Disease-free survival, overall survival, relapse-free survival (all non-inferiority)
Accrual:	3348 accrued
Sponsorship:	Hoffman-La Roche
Status:	Completed
A prospectively randomized study on adjuvant chemotherapy in patients with operated colon carcinoma Dukes B (stage II; T3-4, N0, M0)	
Protocol ID:	NCT00309543
Date last modified:	March 31, 2006
Type of trial:	Randomized, active control, open-label
Primary endpoint:	Overall survival
Accrual:	636 will be accrued
Sponsorship:	Austrian Breast & Colorectal Cancer Study Group
Status:	Completed
Early commencement of adjuvant chemotherapy for colon cancer (ECTX)	
Protocol ID:	NCT01460589
Date last modified:	January 26, 2015
Type of trial:	Randomized, active control, open-label
Primary endpoint:	3-year disease-free survival
Accrual:	198 will be accrued
Sponsorship:	Kyungpook National University
Status:	Enrolling by invitation only

Adjuvant therapy (3 vs. 6 months) with the FOLFOX4 or XELOX for stage II or stage III colon cancer	
Protocol ID:	NCT01308086
Date last modified:	June 21, 2014
Type of trial:	Randomized, active control, open-label
Primary endpoint:	3-year relapse-free survival
Accrual:	2000 will be accrued
Sponsorship:	Hellenic Oncology Research Group
Status:	Recruiting
Combination chemotherapy after surgery in treating patients with high-risk stage II or stage III colorectal cancer	
Protocol ID:	NCT00749450
Date last modified:	April 23, 2012
Type of trial:	Randomized, active control, open-label
Primary endpoint	3-year disease-free survival
Accrual:	9500 will be accrued
Sponsorship:	Cancer Research UK, Glasgow
Status:	Unknown
Combination chemotherapy for 3 months or 6 months in treating patients with stage III colon cancer (IDEA)	
Protocol ID:	NCT00958737
Date last modified:	November 6, 2012
Type of trial:	Randomized, active control, open-label
Primary endpoint	Disease free survival
Accrual:	2000 will be accrued
Sponsorship:	Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR)
Status:	Recruiting
Study investigating the role of oxaliplatin duration in modified FOLFOX6 or CAPOX regimen as adjuvant colon cancer therapy	
Protocol ID:	NCT01092481
Date last modified:	June 12, 2013
Type of trial:	Randomized, active control, open-label
Primary endpoint	3-year disease free survival
Accrual:	2660 will be accrued
Sponsorship:	Samsung Medical Center
Status:	Recruiting
Leucovorin and fluorouracil compared with observation in treating patients with colorectal cancer that has been surgically removed	
Protocol ID:	NCT00005586
Date last modified:	December 17, 2013
Type of trial:	Randomized, open-label
Primary endpoint	All-cause mortality
Accrual:	2500 will be accrued
Sponsorship:	Institute of Cancer Research, United Kingdom
Status:	Completed
A randomized controlled study of postoperative adjuvant chemotherapy or uracil-tegafur (UFT) compared with surgery alone (NSAS-CC)	
Protocol ID:	NCT00152230
Date last modified:	July 6, 2011
Type of trial:	Randomized, parallel assignment, open-label
Primary endpoint	Relapse free survival, overall survival
Accrual:	900 will be accrued
Sponsorship:	Taiho Pharmaceutical Company
Status:	Completed

Randomized study evaluating adjuvant chemotherapy after resection of stage III colonic adenocarcinoma in patients 70 and over (ADAGE)	
Protocol ID:	NCT02355379
Date last modified:	February 3, 2015
Type of trial:	Randomized, parallel assignment, open-label, active control
Primary endpoint	3-year disease-free survival
Accrual:	774 will be recruited
Sponsorship:	Federation Francophone de Cancerologie Digestive
Status:	Recruiting
Low-dose Capecitabine adjuvant chemotherapy for elderly patients with stage II/III colorectal cancer (LcACEC)	
Protocol ID:	NCT02316535
Date last modified:	December 12, 2014
Type of trial:	Randomized, parallel assignment, open label, active control
Primary endpoint	3-year disease-free survival
Accrual:	710 will be accrued
Sponsorship:	West China Hospital
Status:	Enrolling by invitation only

DISCUSSION

Since the publication of the Cancer Care Ontario Program in Evidence-Based Care guidelines for stage II and III colon cancer in 2008, there have been several important studies published that have necessitated revisiting the original recommendations. Therefore a guideline update was undertaken by the GI DSG.

There are now more mature data for the combination of 5-FU/LV/oxaliplatin (Table 6) and the use of oral fluoropyrimidines as an alternative to IV 5-FU/LV (Table 5). Two studies, MOSAIC and NSABP C-07, have compared 5-FU/LV with and without oxaliplatin in populations that included both stage II and III colon cancer [5,6]. The primary endpoint of these studies was DFS in the entire population. Although these studies report outcomes separately for stage II and III patients, these are subset analyses and not necessarily powered to analyze the effect of the addition of oxaliplatin in a specific stage. Therefore, these two trials must be judged as demonstrating the superiority of 5-FU/LV/oxaliplatin over 5-FU/LV alone for patients with stage II and stage III colon cancer. XELOXA only included patients with stage III disease and clearly demonstrates a DFS and OS benefit for the addition of oxaliplatin to an oral fluoropyrimidine (capecitabine) to 5-FU/LV [8].

Although caution must be observed with subset analyses, both MOSAIC [5] and NSABP C-07 [6] report a significant DFS benefit for stage III patients but not stage II patients. Similarly, MOSAIC reports a significant OS benefit in stage III and not stage II patients. MOSAIC also analyzed stage II patients according to degree of risk of recurrence [33]. There was no benefit with respect to DFS and OS for low- or high-risk stage II patients (Table 6). Therefore, treatment of stage II patients is not necessarily warranted, particularly in light of the 12% to 14% chronic (i.e., permanent) sensory neuropathy. These data must be interpreted with caution as the trial was not adequately powered for this analysis.

The definition of "high risk" is not clearly defined in the current TNM staging system nor is there clear consensus in the medical literature. Factors variably reported as independently predictive for high risk of tumour recurrence in patients with resected stage II colon cancer include T4 stage, presence of vascular invasion, and less than 12 nodes sampled. Less consistent factors include male gender, poor differentiation, and bowel obstruction. Putative high-risk molecular markers include aneuploid/tetraploid (non-diploid) DNA, MSS or low-frequency MSI, and maintenance of MMR proteins (hMLH1, hMSH2) by immunohistochemistry [52-67]. Of these many factors, there is current consensus that inadequately sampled nodes (<12), T4 lesions (that includes tumour perforation), and poorly differentiated histology warrant additional consideration for patients with stage II colon cancer.

There are tools available (e.g., Adjuvant! Online, Mayo Numeracy, Oncotype DX, Coloprint) that can be used to estimate risk of recurrence. These tools are based on post hoc analysis of randomized data and, thus, there is an exploratory element to them. They may be useful to model the risk of recurrence in a particular patient; however, they cannot determine how beneficial adjuvant chemotherapy will be. Certainly, they are not a substitute for good clinical judgement and decision making at the individual patient level.

Neurotoxicity with 5-FU/LV/oxaliplatin may be severe, and, although it has a significant reversible component, may leave patients with prolonged and, rarely, severe numbness and paresthesis. In the adjuvant setting, this risk of permanent deficit is of greater importance. Careful patient selection, informed consent, patient monitoring, and dose modification is required.

In addition to factors such as underlying neurological conditions, there may be other factors that lead a physician or patient to avoid 5-FU/LV/oxaliplatin. For patients who are not considered candidates for this combination, the alternatives include 5-FU/LV or an oral fluoropyrimidine (Table 5). Data from the X-ACT trial [11,31] demonstrate that oral capecitabine administered for six months has equivalent efficacy to IV 5-FU/LV. However,

capecitabine results in significantly less diarrhea, stomatitis, neutropenia, nausea/vomiting, and alopecia but significantly more hand-foot syndrome when compared with 5-FU/LV. For those able to take oral therapy, capecitabine is therefore generally preferred over 5-FU/LV due to its toxicity profile and ease of administration. It should also be noted that the X-ACT trial (11,31) used bolus 5-FU which is no longer used in current practice. Infusional 5-FU would be used instead. Data from NSABP C-06 [14] and JCOG0205 [13] demonstrate that oral UFT plus LV has similar efficacy to IV 5-FU/LV. The toxicity profile of UFT was similar to that of 5-FU/LV.

Subgroup analysis based on patient age is available for three trials comparing a fluoropyrimidine with fluoropyrimidine with oxaliplatin. It must be reiterated that subgroup analyses should be interpreted with caution and these studies were underpowered for these comparisons. Patients ≤70 years of age demonstrate a significant DFS advantage over patients >70 years in two oxaliplatin-containing regimen trials; MOSAIC [32] and NSABP C-07 [6]. XELOXA [28], another oxaliplatin trial, also reports a DFS advantage in the younger group of patients although p-values are not provided. Younger patients also demonstrate significantly better OS in MOSAIC [5] and NSABP C-07 [6] than older patients (Table 8). Although these data are derived from underpowered subgroup analyses, the fact that statistically significant benefits were still able to be demonstrated is an indication that the effects are real. X-ACT [11] compares oral versus IV fluoropyrimidines in younger (40 to 69 years) and older (≥70 years) patients. Although they report no p-values, it is unlikely that there is a significant DFS or OS difference based on age owing to the 95% CIs of the HRs, which all cross 1.00 (Table 8).

Microsatellite status (MSI versus MSS) in stage II was examined in one pooled analysis of six RCTs [7]. There was no DFS benefit in either group in those who had adjuvant chemotherapy and those who only had surgery. Interestingly, in the MSI group, those receiving adjuvant chemotherapy demonstrated a significant harm with respect to OS than those who received surgery alone. Although not formally addressed in this guideline, there are data demonstrating increased survival in stage III patients who are MSI high [68]. However, these are not randomized data. It is based on retrospective case series data and has associated serious potential biases.

CONCLUSIONS

Patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy. The recommended treatment option is intravenous 5-FU given with LV and oxaliplatin in the regimens known as FOLFOX or FLOX or oral capecitabine and oxaliplatin in the regimen known as XELOX. This recommendation is based on evidence for improved DFS at five years with oxaliplatin regimens compared with 5-FU/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 intravenous 5-FU/LV. Patients with resected stage II colon cancer should not routinely receive adjuvant chemotherapy. Based on the subgroup analysis available, it is unknown whether patients with high-risk stage II disease would benefit from adjuvant chemotherapy. Patients younger than 70 years of age may derive greater DFS and OS benefit from adjuvant chemotherapy compared with those older than 70 years. Stage II patients who are MSI may have an OS detriment if given adjuvant chemotherapy.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix 2.

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer after Complete Resection: Internal and External Review

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2018, and for details on how this guideline was ENDORSED.

INTERNAL REVIEW

Program in Evidence-Based Care (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 and required changes of both of these panels. The details of these reviews and actions taken are described below. Appendix 2 provides a list of members of the Working Group, RAP and Expert Panel and summarizes conflict of interest declarations for all members. The PEBC conflict of interest policy is available at: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=103568.

Expert Panel Review and Approval

The Gastrointestinal Disease Site Group (GI DSG) acted as the Expert Panel for this document. For approval of the guideline document, 75% of the GI DSG membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, GI DSG members could suggest changes to the document, and make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Of the 29 eligible members of the GI DSG, 23 members cast votes and zero abstained, for a total of 79.3% response. Of those that cast votes, 23 approved the document (100%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses taken in response are summarized in Table 1.

Table 1. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. Change wording in Recommendation 5 from "It would be reasonable…" to "It is reasonable…"	This change was made.
2. To reword Recommendation 5 to include the fact that the recommendation is based on post hoc analysis that have not shown a clear benefit in patients older than 70.	This change was made.

Report Approval Panel Review and Approval

Three RAP members reviewed this document in March and April 2015. The RAP approved the document April 12, 2015. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 2.

Table 2. Modifications/actions/responses regarding main comments from the Report Approval Panel.

Main comments	Modifications, actions, or responses
1. To change the order of the qualifying statements for Recommendation 4.	This change was made.
2. To change the order of the recommendations.	This change was not made. It was believed that organizing the recommendations by stage was the best way to present them.
3. To add a qualifying statement to Recommendation 1 to indicate why a recommendation for high-risk stage II patients was warranted.	A qualifying statement was added.
4. To clarify in the interpretation of evidence for the recommendations that the Working Group's opinion that patients would value survival as the most important outcome was, in fact, just an opinion and not based on patient feedback.	This clarification was made.
5. Reword Question 3b so that it was structured in a better way.	This change was made.
6. To include a statement as to why the data for Question 1 were provided in an Appendix rather than in the Outcomes part of Section 4.	A clarifying statement was added.
7. Several editorial/grammatical changes were suggested.	These suggested changes were made.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes 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. Refer to the PEBC Handbook for additional detail.
(https://www.cancercareontario.ca/sites/ccocancercare/files/PEBCHandbook.pdf)

Targeted Peer Review: Five targeted peer reviewers from Ontario, Alberta, and British Columbia who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Four agreed to be the reviewers. Four responses were received. Their affiliations and conflict of interest declarations are in Appendix 2. Key results of the feedback survey are summarized in Table 3. The main written comments from targeted peer reviewers and the Working Group's modifications/actions/responses are summarized in Table 4.

Table 3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	2
2. Rate the guideline presentation.			1		3
3. Rate the guideline recommendations.			1	1	2
4. Rate the completeness of reporting.				2	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	2
6. Rate the overall quality of the guideline report.				2	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	3
8. I would recommend this guideline for use in practice.				1	3
9. What are the barriers or enablers to the implementation of this guideline report?	Awareness that these guidelines are available and have been updated.				

Table 4. Modifications/actions/responses regarding main written comments from targeted peer reviewers.

Main written comments	Modifications, actions, or responses
1. A comment by several reviewers that tools for assessing risk of recurrence (e.g., Adjuvant! Online or Oncotype DX) were not discussed.	A section addressing this issue was added to the discussion in Section 4.
2. A concern about the phrasing of Question 4.	The phrasing of Question 4 was modified.
3. A concern that Recommendation 3 regarding adjuvant chemotherapy in patient with MSI should be clearer.	A sentence has been added to the recommendation to make it clearer.
4. A comment that there should be some discussion of the data for MSI in Stage III.	This was added to the discussion in Section 4.
5. A comment that the rate of severe neuropathy during oxaliplatin treatment should be included.	This was added in.
6. Several editorial/grammatical changes were suggested.	These suggested changes were made.

Professional Consultation: Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists with an interest in gastrointestinal cancers in the PEBC database were contacted by email to inform them of the survey. A total of 120 respondents were identified. 19 (16%) responses were received. Nine stated that they did not have interest in this area or were unavailable to review this guideline at the time or were retired. The key results of the feedback survey from 10 people are summarized in Table 5. The main comments from the professional consultation and the Working Group's modifications/actions/responses are summarized in Table 6.

Table 5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				4(40)	6(60)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				6(60)	4(40)
3. I would recommend this guideline for use in practice.				5(50)	
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: (1) Knowledge transfer with respect to changing surgeons referrals to medical oncology. (2) Buy in from medical oncologists.				

Table 6. Modifications/actions/responses regarding main written comments from professional consultants.

Main written comments	**Modifications, actions, or responses**
1. A concern that the recommendation that adjuvant chemotherapy in high-risk stage II patients is an option should be much more qualified.	The Working Group believed that this issue was adequately qualified in Sections 1 and 2 and adequately discussed in Section 4.
2. A concern that observation should be recommended for adjuvant therapy in high-risk T4 MSI patients.	The Working Group believed that the treatment of T4 MSI patients was adequately addressed in the Qualifying Statement for Recommendation 3.
3. A comment that it should be noted that the X-ACT trial used bolus 5-FU which is no longer used.	This was added in.

CONCLUSION

This Guideline report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the RAP of the PEBC. Updates of the report will be conducted in accordance with the *PEBC Document Assessment and Review Protocol*.

Appendix 1. Members of the Gastrointestinal Disease Site Group

Members of the Gastrointestinal Disease Site Group

Name	Specialty	Affiliation
Belal Ahmad	RO	London Regional Cancer Program London, ON
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Scott Berry	MO	Odette Cancer Centre Toronto, ON
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Christine Brezden-Masley	MO	St. Michael's Hospital Toronto, ON
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON
Natalie Coburn	SO	Odette Cancer Centre Toronto, ON
Craig Earle	MO	Odette Cancer Centre Toronto, ON
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON
Gregory Knight	MO	Grand River Regional Cancer Centre Kitchener, ON
Jennifer Knox	MO	Princess Margaret Hospital Toronto, ON
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Richard Malthaner	SO	London Regional Cancer Program London, ON
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON
Jason Pantarotto	RO	Ottawa Hospital Cancer Centre Ottawa, ON

Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON
Marko Simunovic	SO	Juravinski Cancer Centre Hamilton, ON
Simron Singh	MO	Odette Cancer Centre Toronto, ON
Stephen Welch	MO	London Regional Cancer Progam London, ON
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON
Youssef Youssef	RO	Durham Regional Cancer Centre Oshawa, ON
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, ON

Notes: HRM, health research methodologist; MO, medical oncologist; RO, radiation oncologist; SO, surgical oncologist

Appendix 2. Members of the stage II and III Colon Cancer Working Group, Expert Panel, Report Approval Panel and Target Reviewers and their conflict of interest declarations.

Members of the Stage II and III Colon Cancer Working Group

Name	Specialty	Affiliation	Declarations of interest
Brandon Meyers Working Group Chair	MO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest.
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest.
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON	Declared they had no conflicts of interest.
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, Ontario	Declared they had no conflicts of interest.

Notes: HRM, health research methodologist; MO, medical oncologist; SO, surgical oncologist

Members of the Stage II and III Colon Cancer Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Belal Ahmad	RO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Within the past five years received $5000 or more in a single year to act in a consulting capacity (Roche, Sanofi, Pfizer, Amgen). Within the past five years received $5000 or more in a single year to fund a research fellow. Within the past five years received grants from Roche, Sanofi, Pfizer, Amgen, Bristol-Meyers Squibb Within the past five years was an investigator for NCIC CRC6 and other trials. Within the past five years, Director of Medical Oncology Fellowship Program.
Scott Berry	MO	Odette Cancer Centre Toronto, ON	Within the past five years received $5000 or more in a single year to act in a consulting capacity (Sanofi, Roche)
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Christine Brezden-Masley	MO	St. Michael's Hospital Toronto, ON	Declared they had no conflicts of interest
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON	Declared they had no conflicts of interest
Natalie Coburn	SO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Craig Earle	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest

Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON	Within past five years received grants from Sanofi and Amgen.
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest
Gregory Knight	MO	Grand River Regional Cancer Centre Kitchener, ON	Within the past five years received $5000 or more in a single year to act in a consulting capacity.
Jennifer Knox	MO	Princess Margaret Hospital Toronto, ON	Within past five years received research grant from Pfizer.
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Richard Malthaner	SO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest
Jason Pantarotto	RO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON	Declared they had no conflicts of interest
Marko Simunovic	SO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Simron Singh	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Stephen Welch	MO	London Regional Cancer Program London, ON	In the past five years received educational grants from Hoffman-LaRoche and Sanofi. Local PI on NCIC CRC6.
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest
Youssef Youssef	RO	Durham Regional Cancer Centre Oshawa, ON	Declared they had no conflicts of interest
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON	Within the past 5 years received a research grant from Sanofi

Notes: MO, medical oncologist; RO, radiation oncologist; SO, surgical oncologist

Members of the Stage II and III Colon Cancer Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Melissa Brouwers	PhD	Director, Program in Evidence-Based Care	Declared they had no conflicts of interest
Bill Evans	MO	Retired	Within the past five years received $5000 or more in a single year to act in a consulting capacity to Roche and Boehringer-Ingelheim. However, there was nothing related to any of the drugs covered in this guidance document.
Donna Maziak	SO	Ottawa General Hospital	Declared they had no conflicts of interest

MO, medical oncologist; RO, radiation oncologist; SO=surgical oncologist

Members of the Stage II and III Colon Cancer Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Parmeet Cheema	MO	Odette Cancer Centre Toronto, Ontario	Within the past five years received $5000 or more in a single year: • to act in a consulting capacity to AstraZeneca and • as a speaker honorarium from Boehringer -Ingelheim Within the past five years has received research support from AstraZeneca, Hoffman La Roche and Boehringer-Ingelheim. Is a voting member of the Ontario Steering Committee for Cancer Drugs (OSCCD).
Sharlene Gill	MO	BC Cancer Agency Vancouver, BC	Within the past five years has been PI for PANCREOX (oxaliplatin in pancreatic cancer) and CRC3 (FOLFOX +/- cetuximab in adjuvant CRC) trials. Has published review articles on adjuvant management of CRC.
Hagen Kennecke	MO	BC Cancer Agency Vancouver, BC	Within the past five years has received research support from Sanofi-Aventis for biomarker assay development.
Vincent Tam	MO	Tom Baker Cancer Centre Calgary, Alberta	Declared they had no conflicts of interest

MO=medical oncologist;

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, GI DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest (see Tables above).

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

Appendix 3. Comparison of staging systems for colorectal cancer.

AJCC	UICC	Modified Astler-Coller	Dukes'
Stage I Tumour invades submucosa T1,N0,M0 Tumour invades muscularis propria T2, N0, M0	Stage I T1-T2,N0,M0	 A B1	 A A
Stage II Tumour invades through muscularis propria into pericolorectal tissues T3,N0,M0 Tumour perforates the visceral peritoneum, or directly invades other organs or structures T4,N0,M0	Stage II T3,T4,N0,MO IIA – T3,N0,M0 IIB – T4a,N0,M0 IIC – T4b,N0,M0	 B2 B2 B3	 B B B
Stage III Any degree of bowel wall with regional node metastasis Any T,N1-N2, M0	Stage III Any T,N1,N2,M0 IIIA T1-T2,N1,M0 T1,N2a,M0 IIIB T3-T4a, N1,MO T2-T3,N2a,M0 T1-T2,N2b,M0 IIIC T4a,N2a,M0 T3-T4a,N2b,M0 T4b,N1-N2,M0	 C1 C2 C1/C2 C1 C2 C2 C3	 C C C C C C C
Stage IV Any invasion of bowel wall, with or without regional lymph node metastasis, but with evidence of distant metastasis Any T, any N,M1	Stage IVA Any T, any N, M1a Stage IVB Any T, any N, M1b		

Note: AJCC, American Joint Commission on Cancer; UICC, International Union Against Cancer.

Appendix 4. Literature search strategy.

MEDLINE

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english

37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. colonic neoplasms/
42. colorectal neoplasms/
43. (colon cancer or cancer of the colon).mp.
44. colonic neoplasms.mp.
45. (colorectal cancer or colorectal neoplasms).mp.
46. chemotherapy, adjuvant/
47. (chemotherapy and adjuvant).mp.
48. or/41-45
49. or/46-47
50. 48 and 49
51. 40 and 50
52. (200709: or 20071: or 2008: or 2009: or 2010: or 2011: or "2012" or “2013”).ed.
53. 51 and 52
54. remove duplicates from 53
55. limit 54 to english

EMBASE

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or Quantitative synthes?s or quantitative overview?).tw.
4. (systematic adj (review$1 or overview$1)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.

19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. exp colon tumor/
37. (colon cancer or cancer of the colon).mp.
38. colonic neoplasms.mp.
39. (colorectal cancer or colorectal neoplasms).mp.
40. or/36-39
41. adjuvant chemotherapy/
42. (chemotherapy and adjuvant).mp.
43. (chemotherapy or systemic therapy).tw.
44. or/41-42
45. 40 and 44
46. 35 and 45
47. (2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ew.
48. 46 and 47
49. remove duplicates from 48

Appendix 5. Abbreviations of names of clinical trials or clinical trials groups.

Abbreviation	Clinical Trial Group
ACCENT	Adjuvant Colon Cancer Endpoints Group
ANZBCTG	Australia and New Zealand Breast Cancer Trials Group
CCCSG (Japan)	Colorectal Cancer Chemotherapy Study Group
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
GIVIO-SITAC	Gruppo Italiano Valutazione Interventi in Oncologia – Studio Italiano Terapia Adiuvante Colon
IMPACT	International Multicentre Pooled Analysis of Colon Cancer Trials
JCOG	Japan Clinical Oncology Group
MOSAIC	Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer
NCCTG	North Central Cancer Therapy Group
NGTATG	Nordic Gastrointestinal Tumour Adjuvant Therapy Group
NSABP (US)	National Surgical Adjuvant Breast and Bowel Project
PETACC	Pan-European Trials in Adjuvant Colon Cancer
QUASAR (UK)	Quick and Simple and Reliable
X-ACT	Xeloda for the Adjuvant therapy for colon cancer
XELOXA	Xeloda plus Oxaliplatin

Appendix 6. Chemotherapy regimens in randomized controlled trials.

Adjuvant chemotherapy versus Observation	
Trial (reference)	**Regimen**
Windle 1987 [27]	5-FU, IV, 1 g following surgery and on first 2 postoperative days, 1 g orally, weekly for 6 months. Levamisole, oral, 150 mg on first 3 postoperative days.
Gray 1987 [1]	5-FU, IV, 600 mg/m^2 per day for 7 days immediately following surgery.
Francini 1994 [9]	Treatment initiated within 3 weeks of surgery. 5-FU, IV, 400 mg/m^2 days 1-5. Folinic acid 200 mg/m^2 days 1-5. Cycle repeated every 4 weeks, for 12 cycles
O'Connell 1997 [26]	5-FU, bolus, 425 mg/m^2 per day for 5 consecutive days. LV, bolus, 20 mg/m^2 immediately preceding each dose of 5-FU. Courses repeated at 4 weeks, 8 weeks, then every 5 weeks for a total of 6 cycles.
Zaniboni 1998 [3]	Chemotherapy initiated within 5 weeks of surgery. 5-FU, 370 mg/m^2 daily for 5 days every 4 weeks for 6 cycles. Folinic acid, 200 mg/m^2 daily for 5 days every 4 weeks for 6 cycles.
Kato 2002[24]	UFT, oral, 400 mg/day, 2 caps twice daily, 2 years.
McDermott 2003 [25]	Folinic acid, 2-hr infusion, 200 mg/m^2, followed by 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 400 mg/m^2 for 2 consecutive days, cycle repeated every 2 weeks for 8 cycles.
Gray 2007 [2]	5-FU, IV, 370 mg/m^2, either six 5-day, 4-weekly, or 30 once-weekly courses. L-folinic acid, either high dose (175 mg) or low dose (25 mg) Levamisole or placebo.
Hamaguchi 2011 [10]	UFT 400 mg/m^2/day, twice daily on 5 consecutive days per week for 1 year.
Schippinger 2007 [4]	5-FU, 450 mg/m^2 plus LV 100 mg/m^2 weekly, weeks 1-6, in 8-week cycles for 7 cycles.

Adjuvant oral fluoropyrimidines versus Intravenous 5-FU	
Trial (reference)	**Regimen**
Twelves 2012 [11] X-ACT	5-FU/LV arm: LV, IV bolus, 20 mg/m^2, followed immediately by 5-FU, IV bolus, 425 mg/m^2 days 1-5, cycle repeated every 28 days, 6 cycles.
	Capecitabine arm: Capecitabine, oral, 1250 mg/m^2, twice daily, days 1-14, cycle repeated every 21 days, 8 cycles.
Lembersky 2006 [14] NSABP C-06	5-FU/LV arm: LV, 2-hr infusion, 500 mg/m^2 and 5-FU, 500 mg/m^2 IV bolus, 1 hr after LV infusion, weekly for six weeks, cycle repeated after 2 weeks rest, 3 cycles.
	UFT + LV arm: UFT, oral, 300 mg/m^2 per day and LV, oral, 90 mg per day, daily doses divided in 3 and taken every 8 hrs, for 4 weeks, cycle repeated after 1 week rest, 5 cycles.
Shimada 2012 [13] JCOG0205	5-FU/I-LV arm: 5-FU, IV, (500 mg/m$^{2)}$ plus I-LV (250 mg/m^2) on days 1, 8, 15, 22, 29, 36, in 8-week cycles for 3 cycles.
	UFT/LV arm: UFT (300 mg/m^2 per day) plus LV (75 mg per day) on days 1-28, in 5-week cycles for 5 cycles.

de Gramont 2012 [12] AVANT	FOLFOX4/Bev arm: Bev (5 mg/kg IV infusion) on day 1 followed by IV oxaliplatin (85 mg/m^2) with IV LV (200 mg/m^2) followed by fluorouracil (400 mg/m^2 bolus then 600 mg/m^2 22-hr continuous infusion). On day 2 IV LV (200 mg/m^2), fluorouracil (400 mg/m^2 bolus then 600 mg/m^2 22-hr continuous infusion) with cycles repeated every 2 weeks for 12 cycles (24 weeks). This was followed by Bev (7.5 mg/kg) on day 1 every 3 weeks for a further 8 cycles (24 weeks).
	XELOX/Bev arm: Bev (7.5 mg/kg IV) followed by oxaliplatin (130 mg/m^2 IV) on day 1 every 3 weeks and capecitabine (1000 mg/m^2 twice daily orally, with first dose in the evening of day 1 and the last dose in the morning of day 15) every 3 weeks for 8 cycles (24 weeks). This was followed by Bev 7.5 mg/kg IV) on day 1 every 3 weeks for a further 8 cycles (24 weeks).
Pectasides 2015 [15]	mFOLFOX6 arm: Oxaliplatin (85 mg/m^2), LV (200 mg/m^2) as a 2-hour infusion, and 5-FU IV bolus (400 mg/m^2) on day 1 followed by 5-FU (2400 mg/m^2) 46-hour continuous infusion, cycle repeated every 14 days for 12 cycles.
	CAPOX arm: Oxaliplatin (130 mg/m^2) on day 1 and capecitabine (1000 mg/m^2) bid on days 1-14, repeated every 21 days for 8 cycles.

Adjuvant 5-FU plus oxaliplatin versus 5-FU	
Trial (reference)	**Regimen**
Andre 2009 [5] MOSAIC	5-FU/LV arm: LV, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles.
	5-FU/LV + oxaliplatin arm: LV, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. Oxaliplatin, 2-hr infusion, 85 mg/m^2 day 1, given simultaneously with LV.
Yothers 2011 [6] NSABP C-07	5-FU/LV arm: 5-FU, IV bolus, 500 mg/m^2, and LV, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles.
	5-FU/LV + oxaliplatin (FLOX) arm: 5-FU, IV bolus, 500 mg/m^2, and LV, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles. Oxaliplatin, IV, 85 mg/m^2, days 1, 15, 29 of each 8-week cycle, 3 cycles.
Schmoll 2012 [8] XELOXA	Bolus 5-FU/LV arm: Mayo clinic, 6 cycles (24 weeks) or Roswell Park, 4 cycles (32 weeks) XELOX arm: Oxaliplatin (130 mg/m^2 given in a 2-hr IV infusion) on day 1 and oral capecitabine (1000 mg/m^2 twice daily) on days 1-14 every 3 weeks for 8 cycles (24 weeks)

Adjuvant 5-FU plus oxaliplatin in stage II versus stage III	
Trial (reference)	**Regimen**
Andre 2009 [5] MOSAIC	5-FU/LV + oxaliplatin arm: LV, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. Oxaliplatin, 2-hr infusion, 85 mg/m^2 day 1, given simultaneously with LV.

Adjuvant 5-FU plus oxaliplatin versus 5-FU or Adjuvant fluoropyrimidine monotherapy in patients less than and greater than 70 years old	
Trial (reference)	**Regimen**
Andre 2009 [5] MOSAIC	5-FU/LV arm: LV, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles.
	5-FU/LV + oxaliplatin arm: LV, 2-hr infusion, 200 mg/m^2, then 5-FU, IV bolus, 400 mg/m^2 and 5-FU, 22-hr infusion, 600 mg/m^2, days 1-2, cycle repeated every 2 weeks, 12 cycles. Oxaliplatin, 2-hr infusion, 85 mg/m^2 day 1, given simultaneously with LV.
Yothers 2011 [6] NSABP C-07	5-FU/LV arm: 5-FU, IV bolus, 500 mg/m^2, and LV, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles.
	5-FU/LV + oxaliplatin (FLOX) arm: 5-FU, IV bolus, 500 mg/m^2, and LV, IV, 500 mg/m^2, weekly for 6 weeks, cycle repeated every 8 weeks, 3 cycles. Oxaliplatin, IV, 85 mg/m^2, weeks 1, 3, and 5 of each 8-week cycle, 3 cycles.
Schmoll 2012 [8] XELOXA	Bolus 5-FU/LV arm: Mayo clinic, 6 cycles (24 weeks) or Roswell Park, 4 cycles (32 weeks) XELOX arm: Oxaliplatin (130 mg/m^2 given in a 2-hr IV infusion) on day 1 and oral capecitabine (1000 mg/m^2 twice daily) on days 1-14 every 3 weeks for 8 cycles (24 weeks)
Twelves 2012 [11] X-ACT	5-FU/LV arm: LV, IV bolus, 20 mg/m^2, followed immediately by 5-FU, IV bolus, 425 mg/m^2 days 1-5, cycle repeated every 28 days, 6 cycles.
	Capecitabine arm: Capecitabine, oral, 1250 mg/m^2, twice daily, days 1-14, cycle repeated every 21 days, 8 cycles.

Appendix 7. Fluoropyrimidine-based systemic chemotherapy versus observation.

Randomized Controlled Trials

Ten randomized controlled trials (RCTs) were obtained that compared a fluoropyrimidine-based systemic chemotherapy regimen with observation alone in patients with resected stage II or III colon cancer (Table 10) [1-4,9,10,24-27]. Only six [1-4,9,10] of the 10 RCTs reported results for patients with stage II and III colon cancer separately in subgroup analyses, and five of the RCTs [2,10,24,25,27] included patients with rectal cancer. One of the 10 RCTs has only been published in abstract form [25]. None of the 10 RCTs reported on blinding, and the randomization method was adequately described in only four studies [2,4,10,24]. Statistical calculations to determine study power and target sample size were reported in six RCTs [2-4,9,10,24], and one study reported that they were statistically underpowered [25]. Two studies were terminated early [4,9].

Disease-Free Survival

Of the five RCTs that reported statistical comparisons for disease-free survival (DFS) data of all study patients [1,3,9,24,26], three of four reported a significant benefit for 5-fluorouracil (5-FU) (with or without leucovorin [LV]) [3,9,26], and zero of one reported a benefit for oral fluoropyrimidines compared with observation alone. Of the three trials that reported comparative DFS data for patients with stage II colon cancer receiving various chemotherapy regimens [1,3,4], none reported a significant benefit for chemotherapy over observation. Of the four trials that reported comparative DFS data for patients with stage III colon cancer [1,3,9,10], two of three reported a significant benefit for 5-FU (with or without LV) [3,9], and zero of one reported a significant benefit for oral fluoropyrimidines compared with observation alone. In general, the evidence suggests a benefit in DFS for adjuvant chemotherapy compared with observation alone in patients with stage III disease but not in patients with stage II disease. No separate DFS data for high-risk and lower risk stage II patients are available.

Overall Survival

Of the eight RCTs that reported statistical comparisons for overall survival (OS) data of all study patients [1-3,9,24-27], four of seven reported a significant benefit for 5-FU (with or without LV) [2,3,9,26]. None of the four trials that reported comparative OS data for patients with stage II colon cancer demonstrated a benefit for adjuvant chemotherapy over observation alone [1-4]. Of the four trials that reported comparative OS data for patients with stage III colon cancer [1,3,9,10], two of three reported a benefit for 5-FU (with or without LV) [3,9], and zero of one reported a benefit for oral fluoropyrimidines over observation. No separate OS data for high-risk and lower risk stage II patients were reported.

Adverse Effects

Of the 10 RCTs that compared fluoropyrimidine-based adjuvant chemotherapy with observation alone, eight reported adverse effects data [2,3,9,10,24-27]. The adverse effects reported in the trials varied according to treatment regimen.

Five RCTs comparing 5-FU, with or without LV, with surgery alone reported data for adverse effects [3,9,25-27]. Toxicity was mainly gastrointestinal, including stomatitis and diarrhea. Grade 3 or 4 toxicities included mucositis in 5.3% of patients [3], diarrhea in 2.4% to 24% [3,25,26], nausea and vomiting in 0.8% to 7% [3,25,26], stomatitis in 36% [26], and leukopenia in 14% [26]. One death possibly related to chemotherapy was reported in the QUASAR trial [2].

Two RCTs reported adverse effects data for oral fluoropyrimidines compared with surgery alone [10,24]. One RCT comparing oral uracil and tegafur (UFT) with observation reported no toxicity of grade 3 or more and no significant difference in incidence of adverse events between treatment

groups [24]. However, another trial comparing UFT with observation reported more grade 3 and 4 toxicities in the UFT arm of the colon cancer subgroup, although no p-values were provided [10].

Quality of Life

Only two of the 10 RCTs that compared fluoropyrimidine-based adjuvant chemotherapy with observation reported data for quality of life outcomes [2,3]. In one trial [3], patients completed self-administered questionnaires at the time of discharge from the treatment centre and at six and 12 months after randomization. Thirty-seven percent of patients completed only the first two questionnaires, and 27% had data available for all three time points. Study coordinators developed the validated questionnaires to evaluate global quality of life, emotional well-being, satisfaction with care, worry about the future, change in social life, impact of disease, and follow-up. No statistically significant difference was found between the patients who received high-dose 5-FU/LV and those who underwent observation alone. In the QUASAR trial [2], quality of life measurements directly related to chemotherapy toxicity (diarrhea, nausea, vomiting, mouth pain, fatigue, appetite loss, and social functioning) were significantly worse during treatment in patients who received chemotherapy compared with patients who underwent observation alone ($p<0.001$).

Table 10. Randomized controlled trials of systemic fluoropyrimidine-based chemotherapy versus observation in patients with stage II and III resected colorectal cancer.

Trial, year (reference)	Treatment allocation	Months on therapy	Number of patients evaluated			Median follow-up (years)	All trial patients		Stage II colon patients		Stage III colon patients	
			Rectal	Colon			DFS%	OS%	DFS%	OS%	DFS%	OS%
				Stage II	Stage III							
5-FU (+ LV)												
Windle 1987 [27]	Observation 5-FU	- 6	19 16	26 26		>5	NR	56 48 p>0.05	NR	NR	NR	NR
Gray 1987 ANZBCT 8201 [1]	Observation 5-FU	- 7 days	- -	232 total		NR	NR p=NS	NR p=0.802	NR P=NS	NR p=NS	NR p=0.341	NR p=0.853
Francini 1994 [9]	Observation 5-FU/LV-ld	- 12	- -	60 59	58 57	4.5	59 74 **p<0.01**	65 79 **p<0.01**	77 83	86 89	41 66 **p<0.01**	43 69 **p<0.01**
O'Connell 1997 NCCTG [26]	Observation 5-FU/LV-ld	- 6	- -	27 30	124 128	6	58† 74† **0.004**	63 74 **p=0.02**	NR	NR	NR	NR
Zaniboni 1998 GIVIO-SITAC 01 [3]	Observation 5-FU/LV-hd	- 6	- -	228 223	218 200	5.25 5.4	54 66 **p<0.001**	65 72 **p=0.02**	68 76 p=0.155**	77 80 p=0.24	37 56 **p<0.001**	51 63 **p=0.03**
McDermott 2003 (abstract) [25]	Observation 5-FU/LV	- 4	127‡ 127‡			6.8	NR	NR p=0.2	NR	NR§	NR	NR§
Gray 2007 QUASAR [2]	Observation 5-FU/LV (high-dose or low-dose LV)††	NR	474 474	1143 1148		5.5	NR	77 81 **p=0.008**	NR	82 84 p=NS	NR	NR
Schippinger 2007 [4]	Observation 5-FU/LV	12.9	-	500	-	8	-	-	p=0.77	p=0.49	-	-
Oral fluoropyrimidines												
Kato 2002 [24]	Observation UFT	24	63 66	81 79		5.9	74 77 ıııı p=0.7087	84 84ıııı p=0.9712	NR	NR	NR	NR
Hamaguchi 2011 [10]	Observation UFT	12	274	-	332	6.2	-	-	-	-	RFS 69.6 71.3 p=0.56	76.7 81.3 p=0.39

Notes: 5-FU, 5-flourouracil; DFS, disease-free survival; LV, leucovorin calcium; LV-hd, high dose LV; LV-ld, low dose LV; NR, not reported; NS, not significant; OS, overall survival; UFT, oral tegafur and uracil.

† Relapse-free survival.

‡ Of 254 total patients, 164 had stage II disease and 90 had stage III disease.

§ For all stage II patients (including rectal), OS was 73% in the Observation group and 76% in the 5-FU/LV group. For all stage III patients, OS was 47% in the Observation group and 51% in the 5-FU/LV group.

**Reported as ≤0.155 in the text of the article.

†† 17.4% of patients in chemotherapy arm also received levamisole.

ıııı Results for all patients with colon cancer.

Published Meta-analyses of Randomized Controlled Trials

In 1988, Buyse et al. conducted a meta-analysis of all English trials of adjuvant therapy for colorectal cancer of all stages [23] (Table 11). Seventeen trials, including a total of 6791 patients with colorectal cancer, compared adjuvant chemotherapy with surgery alone. The pooled results detected no significant difference in the odds of death between treatment and control (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.87 to 1.06). Outcome according to stage could not be examined due to the lack of standardization of staging methods. For the subgroup of patients treated with 5-FU for at least one year, a significant decrease in the odds of death was detected (OR, 0.83; 95% CI, 0.70 to 0.98; p=0.03) when compared with untreated controls.

Three additional meta-analyses were identified that reported pooled OS results of RCTs comparing adjuvant intravenous chemotherapy with observation alone without a separate analysis by disease stage [38,45,46] (see Table 11). Two of the three reports included trials of both colon and rectal cancer patients [38,46] and all three included only patients with stage II or III disease [38,45,46]. All three meta-analyses demonstrated a significant survival benefit for adjuvant chemotherapy over observation. The Zalcberg et al. [46] meta-analysis of 17 RCTs comparing 5-FU-based chemotherapy with observation further analysed trials by dose and suggested a greater survival benefit with higher doses (p=0.02). Analysis by regimen suggested a greater survival benefit for trials of 5-FU plus levamisole compared with no levamisole; however, a multivariate analysis indicated that the effect of levamisole became non-significant after adjusting for dose. Dube et al. [38] conducted a separate analysis for patients with colon cancer in studies with quality scores >50% and demonstrated a mortality OR of 0.80 (95% CI, 0.70 to 0.92; p<0.05), an absolute mortality reduction of 5%. The Sargent et al. [45] meta-analysis of individual patient data from seven randomized controlled trials comparing 5-FU combined with levamisole or folinic acid with observation reported a significant benefit in recurrence-free survival (hazard ratio [HR], 0.68; 95% CI, 0.60 to 0.76; p<0.001) for adjuvant therapy compared with observation. No significant interaction was observed between age and treatment effect for overall or recurrence-free survival.

Four meta-analyses were identified that pooled data from RCTs comparing adjuvant intravenous chemotherapy with observation with separate analyses by disease stage [36,39,40,44] (see Table 11). Three of the four meta-analyses included only patients with colon cancer [36,39,44], whereas one included both colon and rectal cancer [40]. The majority of the evidence demonstrated a benefit for adjuvant therapy in stage III colon cancer but not in stage II disease.

In 1995, the IMPACT investigators pooled individual patient data from three similar RCTs of 5-FU/LV versus observation alone in stage II or III colon cancer [36]. In stage II patients, neither the OS rate nor the DFS rate was significantly different between groups after three years of follow-up. In both the analysis of stage III patients alone and the combined analysis of stage II and III patients, a significant benefit for adjuvant therapy with 5-FU plus LV was reported for OS and for DFS. After up to 10 years of follow-up [41], mortality was not significantly reduced in stage II patients with adjuvant chemotherapy compared with surgery alone, despite a 21% decrease in mortality for adjuvant chemotherapy in the entire study population. In stage III patients, mortality was significantly reduced with adjuvant chemotherapy compared with surgery alone at 10 years of follow-up.

In 1999, the IMPACT investigators conducted another meta-analysis using individual patient data from stage II patients from five RCTs of 5-FU plus LV compared with observation (IMPACT 2) [37]. Median follow-up of these patients was 5.75 years. There was no significant difference in five-year event-free survival or OS for 5-FU plus LV compared with observation.

Using the database developed by Sargent et al. [45], Gill et al. [39] performed an analysis based on a Cox proportional hazards model. Prognostic factors considered were

adjuvant treatment, age, gender, tumour location, T stage, nodal status, and tumour grade. Only nodal status, T stage, and tumour grade were identified as independently significant prognostic factors for both DFS and OS. Age greater than or less than 60 was a significant prognostic factor only for OS. A 30% proportional reduction in risk of recurrence (HR, 0.70; 95% CI, 0.63 to 0.78) and a 26% proportional reduction in risk of death (HR, 0.74; 95% CI, 0.66 to 0.83) were reported for patients who received adjuvant treatment compared with those who were randomized to surgery alone.

Glimelius et al. [40] reported a pooled analysis of RCTs run in parallel by the NGTATG of adjuvant chemotherapy versus observation in patients with stage II or III colon cancer. Patients in the adjuvant therapy group received 5-FU plus levamisole, 5-FU/LV, or 5-FU/LV plus levamisole. Patients were analyzed after a minimum follow-up of five years. No significant difference in five-year OS was detected between treatment groups for stage II patients or stage III patients.

The authors of the ACCENT group [44] conducted an individual patient data meta-analysis on 20,898 patients from 18 trials of adjuvant therapy in stage II and III colon cancer. A subset of 4922 patients from nine trials compared surgery plus 5-FU-based chemotherapy with surgery alone. Eight-year OS was significantly better in the chemotherapy arm for all patients ($p<0.001$), stage II patients ($p=0.026$), and stage III patients ($p<0.0001$).

Oral Chemotherapy Versus Observation

Two meta-analyses by Sakamoto et al. using individual patient data to compare oral adjuvant chemotherapy with observation in patients with resected stage I to stage III colorectal cancer were retained [42,43] (see Table 11). They included RCTs comparing adjuvant oral fluoropyrimidines in general with observation. In 1999, a meta-analysis of three RCTs performed in the 1980s comparing adjuvant oral fluoropyrimidines with observation that randomized patients by sealed envelopes reported no significant benefit for oral fluoropyrimidines over observation alone on DFS or OS in the overall analysis of colon cancer patients or the subgroup analyses by disease stage [42]. In 2004, a meta-analysis of three RCTs performed in the 1980s with the same comparison but that randomized patients by centralized randomization was completed [43]. At five years, a marginally significant benefit favouring adjuvant oral chemotherapy was detected in both and for patients with colon cancer. Results for colon cancer patients by disease stage were not reported separately.

Table 11. Published meta-analyses of randomized controlled trials comparing adjuvant chemotherapy with observation.

Author, year (reference)	Patient population	# of RCTs (# of patients)	Treatment allocation	All patients		Stage II colon patients		Stage III colon patients	
				DFS	OS	DFS	OS	DFS	OS
Intravenous chemotherapy									
Buyse 1988 [23]	Colorectal cancer	17 (6791)	Adjuvant CT Observation	NR	OR, 0.96; 95% CI, 0.87-1.06*	NR	NR	NR	NR
IMPACT 1 1995 [36] *(3-year follow-up)*	Stage II and III colon cancer	3 (1493) IPD	High dose 5-FU/LV Observation	HR 0.65; 95% CI 0.54 to 0.78; p<0.0001‡	HR, 0.78; 95% CI 0.62-0.97; p=0.029‡	HR 0.84; 95% CI 0.62-1.12	HR 0.91; 95% CI 0.63-1.34	HR 0.55; 95% CI, 0.44-0.70, p<0.05	HR 0.70; 95% CI 0.53-0.92, p<0.05
Update Marsoni 2001 [41] (*10-year follow-up)*				NR	HR 0.79; p=0.013	NR	HR 0.92; p=0.658	NR	HR 0.70; p=0.003
IMPACT 2 1999 [37]	Stage II colon cancer	5 (1016) IPD	5-FU/LV Observation	-	-	HR, 0.88; 90% CI, 0.72-1.07; p=0.137§	HR, 0.86; 90% CI, 0.68-1.07; p=0.130§	-	-
Zalcberg 1996 [46]	Dukes B and C colorectal cancer	17 (NR)	5-FU-based CT Observation	NR	OR 0.82; 95% CI, 0.74-0.91; p<0.001	NR	NR	NR	NR
Dube 1997 [38]	Dukes C colon and Dukes B or C rectal cancer	29 (12,079)	Adjuvant CT Observation	NR	OR 0.91 95% CI, 0.83-0.99; p<0.05	NR	NR	NR	NR
Sargent 2001 [45]	Stage II or III colon cancer	7 (3351)	5-FU (plus LEV or LV) Observation	NR	HR 0.76; 95% CI, 0.68-0.85; p<0.001	NR	NR	NR	NR
Gill 2004 [39]	Stage II or III colon cancer	7 (3302)	5-FU (plus LEV or LV) Observation	HR 0.70; 95% CI, 0.63-0.78	HR, 0.74; 95% CI, 0.66-0.83	HR 0.831, p=0.0490	HR 0.855, p=0.1127	p<0.05	p<0.05
Glimelius 2005 [40]	Stage II or III colorectal cancer	(2211)	5-FU (plus LEV or LV) Observation	NR	NR	NR	5-year OS p=0.81	NR	5-year OS p=0.15
Sargent 2009 (ACCENT) [44]	Stage II or III colon cancer	9 (4922)∞	Adjuvant CT Observation	NR	8-year OS p<0.001	NR	8-year OS p=0.026	NR	8-year OS p<0.0001

Author, year (reference)	Patient population	# of RCTs (# of patients)	Treatment allocation	All patients		Stage II colon patients		Stage III colon patients	
				DFS	OS	DFS	OS	DFS	OS
Oral chemotherapy									
Sakamoto 1999 [42]	Stage I-III colorectal cancer	3 (4960) IPD¶	Oral fluoropyrimidines Observation	p=0.242†	p=NS†	p=0.296	p=0.721	p=0.0863	p=0.417
Sakamoto 2004 [43]	Stage I-III colorectal cancer	3 (5233) IPD¶	Oral fluoropyrimidines Observation	HR=0.87; 95% CI, 0.75-1.00†	HR=0.86; 95% CI, 0.73-1.00†	NR	NR	NR	NR

Notes: 5-FU, 5-fluorouracil; CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; IPD, individual patient data; LEV, levamisole; LV, leucovorin; NR, not reported; NS, not significant; OR, odds ratio; OS, overall survival; RCT, randomized controlled trial

* For patients who received 5-FU for at least 1 year, OR, 0.83; 95% CI, 0.70 to 0.98; p=0.03.

† Data are for colon patients only

‡ Stratified by stage and country

§ Stratified by age and grade

∞This is the subset that represents surgery + chemotherapy versus surgery alone. The entire ACCENT study included 20,898 patients from 18 trials.

¶ 1999 publication pooled 3 RCTs randomized using sealed envelopes and the 2004 publication pooled 3 RCTs that used central randomization.

Appendix 8: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2008	1987-2007	Full Report	Clin Oncol. 2011;23(5):314-22 Web publication	N.A.
Version 2 2015	2007 to 2014	New data added to original full report	Updated web publication.	Stage II • When treated with adjuvant therapy, high-risk stage II patients should receive a fluoropyrimidine. There are insufficient data to support that oxaliplatin provides additional benefit to all high-risk stage II patients. • Adjuvant chemotherapy with a fluoropyrimidine monotherapy regimen following surgery in patients who have microsatellite instability (MSI) is not recommended. MSI testing should be performed for all stage II patients for whom adjuvant chemotherapy is being considered. In patients with high-risk stage II colon ca (e.g., T4) ***and*** high MSI status (a low risk factor) the choice of treatment is between observation and FOLFOX but data are lacking to guide this decision. Stage III • It would be reasonable to consider FOLFOX for fit older patients as part of an informed discussion between patients and their medical oncologists regarding treatment options.

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Evidence-Based Series 2-29 Version 4: Section 6

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection

Guideline Review Summary

B. Meyers, X. Yao, and Members of the Gastrointestinal Cancer Disease Site Group

February 6, 2024

The 2015 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Program in Evidence-based Care, Ontario Health (Cancer Care Ontario) in 2008, and updated in 2015 and 2019.

In December 2021, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (XY) conducted an updated search of the literature. One clinical expert (BM) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed, with the addition of new qualifying statements. An Expert Panel comprised of members of the Gastrointestinal Cancer Disease Site Group (See Appendix 1 for membership) endorsed the recommendations found in Sections 1 and 2 on February 6, 2024.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1) What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy versus observation on disease-free survival (DFS) and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

2) What is the impact of adjuvant intravenous (IV) 5-FU versus oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

3a) What is the impact of adjuvant fluoropyrimidines versus fluoropyrimidines plus oxaliplatin on DFS and OS in patients with:

i. stage II or III colon cancer who have undergone complete resection with curative intent?
ii. stage II colon cancer who have undergone complete resection with curative intent?
iii. stage III colon cancer who have undergone complete resection with curative intent

3b) What is the impact on DFS and OS of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in patients with stage II versus III colon cancer who have undergone complete resection with curative intent?

4a) What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

4b) What is the impact of adjuvant fluoropyrimidine monotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

5) 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

Target Population:
Adult patients with stage II and III colon cancer who have undergone complete resection with curative intent as primary therapy.

Study Section Criteria:
Inclusion Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:
1) Fully published reports or published abstracts of randomized controlled trials (RCTs) or fully published reports of 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 comparisons listed in the guideline questions.
2) The primary outcome of interest was DFS. Secondary outcomes of interest were OS, treatment toxicity, and quality of life. Articles had to report data for one of these outcomes. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.
3) English-language publications.

Exclusion Criteria:
Articles were excluded for the following reason:
1. Letters, editorials, notes, case reports, and commentaries were not eligible.

Literature Search and New Evidence
This guideline includes literature from the original search (1987 to September 2007), the first update (Version 2; September 2007 to August 2015), and the second update (Version 3; August 2015 to May 2018). A new search was conducted from May 2018 to May 2023 (the search strategy is shown in Appendix 2). The updated search yielded seven full text articles and one conference abstract for a total of 7 RCTs. The evidence is summarized in Table 1.

New Evidence and Impact on the Guideline and Its Recommendations
For research question 1, two new RCTs met the study selection criteria. However, one RCT (JOCCRC trial) did not have a full text publication for the efficacy outcomes [1,2]. No response was obtained from the authors. Another RCT (ECOG-E1292) terminated early due to slow accrual

and was redesigned for patients with stages IIC and III colon cancer. However, data available including stage IIA-IIB as of 19 February 2015 showed that compared with no adjuvant chemotherapy, 7-day 5-FU treatment after standard surgery did not lead to a statistically significant difference in DFS and OS between the two groups in patients with stage II or III colon cancer [3].

For research question 2, the ACHIEVE-2 trial reported there was no statistically significant difference in DFS between 3-month and 6-month adjuvant chemotherapy with fluorouracil, leucovorin, and oxaliplatin in stage II patients (HR = 0.85; 95% CI, 0.23 to 3.16), or between 3-month and 6-month capecitabine and oxaliplatin treatment (HR = 1.13; 95% CI, 0.65 to 1.96) [4]. The HORG-IDEA trial found similar results in stage II and III patients [5].

For research question 4, three RCTs met the inclusion criteria. The Achieve trial conducted in Japan reported no statistically significant difference in OS between 6-month fluoropyrimidine plus 3-month oxaliplatin adjuvant therapy and 6-month fluoropyrimidine plus 6-month oxaliplatin adjuvant therapy in stage III patients (HR = 0.91; 95% CI, 0.69 to 1.20; p=0.51). The subgroup analysis reported that there was no statistically significant difference between the two groups in patients <70 years ≥70 years, respectively; and the p-value was 0.71 for the interaction test, which means that age is not a confounder [6]. However, the TOSCA trial conducted in Italy indicated that stage III patients ≥70 years had worse PDF (HR = 1.34; 95% CI, 1.12 to 1.59; p=0.001) and worse OS (HR = 1.58; 95% CI, 1.26 to 1.99; p=0.51) outcomes than patients <70 years [7]. The JFMC37-0801 trial met the inclusion criteria and reported the subgroup analyses by age less than and greater than 70 years, it compared 16 cycles versus 8 cycles of oral capecitabine, which is not meaningful in current clinical practice [8].

No new evidence was found pertaining to research questions 3 and 5.

The new data support the existing recommendations, however, a qualifying statement has been added to highlight new evidence regarding subgroup analyses by patient age. The qualifying statement for high-risk stage II patients has also been added to the recommendation for stage III patients: In patients with high-risk stage III colon cancer ***and*** high MSI/dMMR status (a low risk factor), the choice of treatment is between observation and oxaliplatin-based chemotherapy, but data are lacking to guide this decision. Furthermore, “FOLFOX”, “FLOX”, or “XELOX” have been changed to “oxaliplatin-based chemotherapy” throughout the recommendations in sections 1 and 2.

Ontario Health
Cancer Care Ontario

Document Review Tool

Number and Title of Document under Review	2-29v3 Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection
Original Report Date	September 25, 2019
Date Assessed (by DSG or Clinical Program Chairs)	December 15, 2021
Health Research Methodologist	Xiaomei Yao
Clinical Expert	Brandon Meyers
Approval Date and Review Outcome (once completed)	February 6 2024

1.Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2.Does the newly identified evidence support the existing recommendations?	Yes.
3.Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes, with an additional Qualifying Statement for Recommendation 5.

Review Outcome as recommended by the Clinical Expert	ENDORSE.
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	

DSG/Expert Panel Commentary	

Evidence Table (Black words for mixed patients; purple for stage II; green for stage III)

Author year (Trial name); Recruited year	Patient population	Intervention: Experimental group (EG) vs. Control group (CG)	DFS Follow-up time: Median time /survival rate; HR (95% CI), p-value	OS Follow-up time: Median time/survival rate, HR (95% CI), p-value	Grade 3 or higher adverse effects
Question 1) What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy versus observation on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?					
Zhang 2017 (IOCCRC trial) for safety outcomes, Zhang 2019 (conference abstract) for efficacy outcomes[a]; 2011-2016	Pts aged 18-75 years with colorectal cancer receiving curative resection (n=178 (26%) rectal cancer, n=507 (74%) colon cancer; n=113 (16%) pts with stage I, n=6 (1%) pts with stage IV.	**EG:** (n=341) Intraoperative chemotherapy group had 1000 mg/m^2 5-FU injected into the lumen and 200 mg/m^2 injected into the mesenteric vein. Before closing the abdominal cavity, 300 mg/m^2 5-FU and 250 mL saline were poured into the cavity. **CG:** (n=344) standard surgery procedure.	3-year DFS with a median follow-up of 65.1 months: **EG:** 21 pts died, 39 pts experienced distance metastasis or local recurrence. **CG:** 26 pts died, 47 pts experienced distance metastasis or local recurrence. p=0.334.	NR.	**EG:** 17 pts experienced a grade 3 or higher adverse event. The only grade 3 or higher adverse events were neutropenia. **CG:** 16 pts experienced a grade 3 or higher adverse event. The only grade 3 or higher adverse events were neutropenia.
Kemeny 2023[b] (ECOG-E1292); 1993-2000	Pts 18+ with resected dukes B3 or C colon cancer (stage IIC or III). Pts 18+ with resected Dukes' B2 colon cancer (stage IIA or IIB).	**EG:** (n=156 for stage IIC or III; n=150 for stage IIA or IIB): continuous infusion of 5-FU for 7 days (600 mg/m^2 /day). **CG:** (n=158 for stage IIC or III; n=139 for stage IIA or IIB): no perioperative 5-FU.	Stage IIC or III: At median 15.4 years: HR=1.04, 95% CI, 0.71 to 1.51; p=0.847. stage IIA or IIB: At Median 15.8 years: p=0.866.	At median follow-up 15.4 years (0.03-20.3): Stage IIC or III: At median 15.4 years (0.03-20.3) HR=0.88; 95%CI, 0.66 to 1.16; p=0.178. Stage IIA or IIB: EG: 16.1 (13.2, -) CG: 12.9 (10.7, -) p=0.243.	**EG:** 47 pts experienced a maximum grade 3 toxicity and 25 grade 4 toxicity. Anemia, diarrhea, and stomatitis were most frequently reported. **CG:** 3 pts grade 3 events.
Question 2) What is the impact of adjuvant intravenous (IV) 5-FU versus oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?					
Yamazaki 2021 (ACHIEVE-2 trial); 2014-2017	Asian pts with high-risk stage II colon cancer.	mFOLFOX6 group (n=82): intravenously administering 85 mg/m^2 oxaliplatin and 200 mg/m^2 *l*-leucovorin in a 2-hour infusion and 400 mg/m^2 bolus fluorouracil on day 1, with 2400 mg/m^2 of fluorouracil infused over 46 hours from days 1 to 3. This was repeated every 14 days. Pts were randomized to take this management either for 3 months (n=40) or 6 months (n=42). CAPOX group (n=432): a 2-hour intravenous infusion of 130 mg/m^2	At median 3 years: mFOLFOX6 group: 88.6% (treatment for 3 months) vs. 85.7% (treatment for 6 months); HR=0.85; 95% CI, 0.23 to 3.16; p=NR. CAPOX group: 88.2% (treatment for 3 months) vs. 88.4% (treatment for 6 months); HR=1.13; 95% CI, 0.65 to 1.96; p=NR.	NR.	mFOLFOX6 group: 28 pts (10 in 3-month group) experienced a hematological event and 9 pts (1 in 3-month group) experienced a non-hematological event. Neutropenia and leucopenia most commonly reported. CAPOX group: 67 pts (29 in 3-month group) experienced a hematological event and 78 (25 in 3-month group) experienced a non-hematological event. Neutropenia, thrombocytopenia, and anorexia most commonly reported.

		oxaliplatin on day 1 and 1000 mg/m^2 oral capecitabine twice daily from the evening of day 1 to the morning of day 15. This was repeated every 21 days. Pts were randomized to take this management either for 3 months (n=215) or 6 months (n=217).			
Souglakos 2019 (HORG-IDEA study); 2009-2015	Pts aged older than 18 years with stage III or high-risk stage II colon cancer and received surgery less than 8 weeks ago.	EG: FOLFOX4 (n=391), 6 or 12 cycles (3 or 6 months). CG: (n=724) CAPOX, 4 or 8 cycles (3 or 6 months).	3-year DFS with a median follow-up of 67.0 months: Stage II pts: FOLFOX4 (3 months vs 6 months): 76.7% vs 79.3%; HR=1.21; 95% CI, 0.54 to 2.70; p=NR. CAPOX (3 months vs 6 months): 85.4% vs 83.8%; HR=0.99; 95% CI, 0.59 to 1.67; p=NR. Stage III pts: FOLFOX4 (3 months vs 6 months): 71.5% vs 77.3%; HR=1.18; 95% CI, 0.74 to 1.86; p=NR. CAPOX (3 months vs 6 months): 74.5% vs 74.7%; HR=1.01; 95% CI, 0.69 to 1.43; p=NR.	NR.	NR.
Question 3) a) What is the impact of adjuvant fluoropyrimidines versus 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?					
None					
b) What is the impact on DFS and OS of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy in patients with stage II versus III colon cancer who have undergone complete resection with curative intent?					
None					
Question 4 a) What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?					

Yoshino 2022 Achieve Trial August 1, 2012, and June 30, 2014	Pts ≥20 years old with stage III low-risk or high-risk colon cancer[a].	EG: 6 months of fluoropyrimidine + 3 months of oxaliplatin adjuvant therapy (n=650). CG: 6 months of fluoropyrimidine + 6 months of oxaliplatin adjuvant therapy (n=641).	NR.	At median follow-up 74.7 months: 5 year OS: Overall: 87% vs. 86.4%; HR=0.91; 95% CI, 0.69 to 1.20; p=0.51. For pts < 70 years[c], EG vs. CG: HR=0.87; 95% CI, 0.62 to 1.24. For pts ≥70 years[c], EG vs. CG: HR=0.97; 95% CI, 0.62 to 1.54. Interaction test: p=0.71.	**During treatment:** Grade 2 or 3 peripheral sensory neuropathy: 84 (13%) and six (1%) pts in EG, and 195 (30%) and 38 (6%) in CG; OR=0.281; 95% CI, 0.214 to 0.370; p=.0001). HFS at any grade was higher in pts who received CAPOX than mFOLFOX6: 432 (45%) vs. 64 (20%); OR=3.243; 95% CI, 2.399 to 4.385; p=0.0001. In the CAPOX group, 6-month compared with 3-month treatment group at grade 3: 15 (3%) vs. 4 (0.8%); OR=3.878; 95% CI, 1.278 to 11.772; p=0.017. **Lasting for more than 5 years:** PSN of any grade was more common in pts with mFOLFOX6: 19 (14%) vs. 48 (11%) with CAPOX; OR=1.380; 95% CI, 0.780 to 2.443; p=0.27.
Rosati 2021 (TOSCA trial); 2007-2013	Pts with stage III colon cancer.	Subgroup analysis from TOSCA trial. G1: n=693, ≥70 years; 227 received FOLFOX-4 for 6 months, 122 received Xelox for 6 months, 225 received FOLFOX-4 for 3 months, and 119 received Xelox for 3 months. G2: n=1667, <70 years; 563 received FOLFOX-4 for 6 months, 294 received Xelox for 6 months, 527 received FOLFOX-4 for 3 months, and 283 received Xelox for 3 months.	At median 61.8 months: G1 vs. G2 (multivariable analysis): HR=1.34; 95% CI, 1.12 to 1.59; p=0.001.	At median 61.8 months: G1 vs. G2 (multivariable analysis): HR=1.58; 95% CI, 1.26 to 1.99; p=<0.001.	At median 61.8 months: G1: 193 (28.3%) pts experienced a grade 3 neurological toxicity. G2: 395 (24.2%) pts experienced a grade 3 neurological toxicity.
b) What is the impact of adjuvant fluoropyrimidine monotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?					

Tomita 2019 JFMC37-0801 study Sept 2008 – Dec 2009	Pts with resected stage III colorectal cancer.	Oral capecitabine 1250 mg/m^2 twice daily after meals for 14 consecutive days followed by 7-day rest. EG: 16 cycles (n=650; n=442 <70 years, n=208 ≥70 years). CG: 8 cycles (n=654; n=451 <70 years, n=203 ≥70 years).	At median follow-up 60.6 months: 5-year DFS: For age < 70 years: HR=0.850; 90% CI, 0.700 to 1.032. For age ≥ 70 years: HR=0.920; 90% CI, 0.701 to 1.208.	NR.	The incidence of overall grade 3–4 adverse events was almost comparable in both groups.
Question 5) 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?					
None					

Abbreviations: 5-FU, fluorouracil; CAPOX, chemotherapy regimen with capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX4, chemotherapy regimen with fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; mFOLFOX6, chemotherapy regimen with fluorouracil, leucovorin, and oxaliplatin; NR, not reported; OS, overall survival; Pts, patients; RT, radiation therapy; S-1, oral fluoropyrimidine used in chemotherapy consisting of tegafur, gimeracil, and oteracil potassium; SOX, S-1 plus oxaliplatin; UFT/LV, capecitabine, tegafur-uracil, and leucovorin; XELOX, chemotherapy regimen with capecitabine and oxaliplatin.

[a] We contacted authors for further fulltext publication info, but there was no response. In the clinicaltrial.gov website, it indicated that this RCT was completed in 2019.

[b] This trial was terminated earlier due to slow accrual but redesigned for patients with stages IIC and III. However, the authors still reported the outcomes for patients with stage IIA-IIB. This report was based on data available as of 19 February 2015.

[c] The HRs with their 95% CIs were measured based on Figure 4 in the original paper.

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Authors		
Brandon Meyers	Clinical Expert Medical Oncologist Gastrointestinal Cancer Disease Site Group	None declared
Xiaomei Yao	Health Research Methodologist Program in Evidence-Based Care	None declared
Expert Panel		
Asma Ali	Health Science North, Sudbury Medical Oncologist	None declared
Sami Chadi	University Health Network – Toronto General and Colerectal Surgery	$500 or more in a single year to act in a consulting capacity from Stryker Endoscopy and Noah Medical
John Lenehan	Medical Oncologist London Health Sciences Centre	None declared
Elan Panov	Medical Oncologist Trillium Health Partners, Credit Valley Hospital	None declared
Michael Sanatani	London Health Sciences Centre Medical Oncologist	None declared

Appendix 2. Search Strategies for Medline and Embase

Database(s): Embase 1996 to 2023 May 25, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to May 25, 2023.

Search Strategy:

#	Searches
1	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp randomized controlled trials as topic/ or exp controlled clinical trial/ or "controlled clinical trial (topic)"/ or controlled clinical trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treble$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (rct or phase III or phase IV or phase 3 or phase 4 or randomi$: or randomly).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
2	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or (meta-analy: or metaanaly: or meta analy:).mp. or (systematic review: or systematic overview:).mp. or ((exp "review"/ or exp "review literature as topic"/ or review.pt. or review:.tw. or overview:.tw.) and (systematic: or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or (study adj selection) or Cochrane or Medline or Embase or PubMed or Med-line or Pub-med or hand search: or hand-search: or manual search: or reference list: or bibliograph: or pooled analys: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s).tw.)
3	exp practice guideline/ or exp guideline/ or guideline.pt. or practice guideline:.mp. or (guideline: or recommend:).ti,kw.
4	2 not 1
5	3 not (1 or 2)
6	exp colon tumor/ or exp colorectal neoplasms/ or (((colon or colonic or colorectal) adj (cancer: or tumor: or tumour: or neoplasm:)) or cancer of the colon).mp.
7	adjuvant chemotherapy/ or (chemotherapy and adjuvant).mp. or (chemotherapy or systemic therapy).tw,kw. or Fluoropyrimidine:.tw,kw. or 5-FU.tw,kw. or 5-fluorouracil.tw,kw. or oxaliplatin.tw,kw.
8	6 and 7
9	(comment or news or newspaper article or case reports or historical article).pt.
10	(editorial or note or letter or short survey).pt. or letter/ or case study/
11	9 or 10

12	exp animals/ not humans/
13	11 or 12
14	(201805: or 201806: or 201807: or 201808: or 201809: or 20181: or 2019: or 2020: or 2021: or 2022: or 2023:).ed. or (201805: or 201806: or 201807: or 201808: or 201809: or 20181: or 2019: or 2020: or 2021: or 2022: or 2023:).dd. or (201805: or 201806: or 201807: or 201808: or 201809: or 20181: or 2019: or 2020: or 2021: or 2022: or 2023:).em.
15	(1 and 8 and 14) not 13
16	remove duplicates from 15

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website and each page is watermarked with the words "ARCHIVE."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

APPENDIX A: DOCUMENT ASSESSMENT AND REVIEW CONDUCTED IN 2019

Evidence-Based Series 2-29 Version 3: Section 6

Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection

Guideline Review Summary

B. Meyers, LD. Durocher-Allen, and Members of the Gastrointestinal Cancer Disease Site Group

September 25, 2019

The 2015 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2007 and updated in 2015.

On November 23, 2017, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (LDA) conducted an updated search of the literature. One clinical expert (BM) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed, with the addition of new qualifying statements. An Expert Panel comprised of members of the Gastrointestinal Cancer Disease Site Group (See Appendix 1 for membership) endorsed the recommendations found in Sections 1 and 2 on September 25, 2019.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1) What is the impact of adjuvant fluoropyrimidine-based systemic chemotherapy versus observation on disease-free survival (DFS) and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

2) What is the impact of adjuvant intravenous (IV) 5-FU versus oral fluoropyrimidines on DFS and OS in patients with stage II or III colon cancer who have undergone complete resection with curative intent?

3a) What is the impact of adjuvant fluoropyrimidines versus fluoropyrimidines plus oxaliplatin on DFS and OS in patients with:

i. stage II or III colon cancer who have undergone complete resection with curative intent?
ii. stage II colon cancer who have undergone complete resection with curative intent?
iii. stage III colon cancer who have undergone complete resection with curative intent

3b) 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?

4a) What is the impact of the addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

4b) What is the impact of adjuvant fluoropyrimidine monotherapy, on DFS and OS, in younger versus older (≤70 years versus >70 years) stage II or III colon cancer patients who have undergone complete resection with curative intent?

5) 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

Target Population:
Adult patients with stage II and III colon cancer who have undergone complete resection with curative intent as primary therapy.

Study Section Criteria:

Inclusion Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:
1) Fully published reports or published abstracts of randomized controlled trials (RCTs) or fully published reports of 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 comparisons listed in the guideline questions.
2) The primary outcome of interest was DFS. Secondary outcomes of interest were OS, treatment toxicity, and quality of life. Articles had to report data for one of these outcomes. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.
3) English-language publications.
4) The clinical trials were published after 1987. Buyse et al. [23] summarized the results of randomized trials of adjuvant therapy for colorectal cancer up to 1987. The results of this meta-analysis are reviewed at the beginning of the Results section.

Exclusion Criteria:
Articles were excluded for the following reasons

1. Letters, editorials, notes, case reports, and commentaries were not eligible.

Literature Search and New Evidence

The original search (from 1987-September 2007) and first update (Version 2; from September 2007-August 2015. A new search was conducted from August 2015 to May 2018 (search strategy is shown in Appendix 2). The updated search yielded 4 practice guidelines, 1 systematic review, and 9 publications of primary studies and abstracts. The evidence is summarized below in Tables 1 to 4.

New Evidence and Impact on the Guideline and Its Recommendations

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration was a prospective, preplanned, pooled analysis of six phase 3 trials that were conducted concurrently and evaluated the noninferiority of three versus six months of oxaliplatin-based therapy (either CAPOX or FOLFOX) in patients with stage III colon cancer [1]. The six trials were: SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand), TOSCA (Italy), CALGB/SWOG 80702 (US, Canada), IDEA (France), ACHIEVE (Japan), and HORG (Greece). For the primary pooled analysis, only stage III colon cancer patients were included, however, some trials included stage II (TOSCA, SCOT, HORG) and rectal cancer patients (SCOT). Most trials allowed investigators to choose CAPOX or FOLFOX (FOLFOX4: TOSCA, HORG; mFOLFOX6: SCOT, IDEA France, 80702, ACHIEVE), whereas mFOLFOX6 was the only regimen used in trial 80702. The primary end point of the six trials was disease free survival (DFS) at three years, and noninferiority of three versus six months could be claimed if the upper limit of the two-sided 95% confidence internal (CI) of the hazard ratio (HR) did not exceed 1.12. The primary analysis in the overall study population resulted in a DFS HR of 1.07 (95% CI 1.00 to 1.15); the noninferiority of three months of treatment versus six months could not be confirmed. Noninferiority of three months of treatment was seen for CAPOX (HR 0.95; 95% CI, 0.85 to 1.06), but not FOLFOX (HR 1.16, 95% CI 1.06 to 1.26). In preplanned subgroup analyses for stage of tumour penetration (T) and nodal status (N), three months of therapy was noninferior to six months in patients with T1-3, N1 cancers (HR 1.01, 95% CI 0.90 to 1.12). Among patients with stage T4, N2, or both, six months' duration was superior to three months (HR 1.12, 95% CI 1.03 to 1.23).

We are aware of recent pooled analysis from the IDEA collaboration that may inform decisions on the duration of treatment in patients with stage II disease [2].

Our interpretation of the new evidence is that for patients with low-risk disease (T1-3 N1), three months of oxaliplatin/fluoropyrimidine-based doublet chemotherapy strikes a reasonable balance between efficacy and neurotoxicity of oxaliplatin; however some patients are not suitable for this regimen. For patients with higher risk (i.e., T4 or N2), six months of oxaliplatin-based chemotherapy may be more reasonable than three months of treatment. Unanswered questions remain as to why there is an effect of regimens, and whether the "ideal" duration is between three and six months. We felt that from a patient perspective, assessing side effects of therapy and making a final determination of duration was important, in addition to a discussion regarding risks and benefits of the regimens.

The new data support the existing recommendations, but qualifying statements have been added to highlight the above.

Clinical Expert Interest Declaration: Dr. Meyers reported that he received $5,000 or more in a single year to act in a consulting capacity as Advisory board participations for Celgene, Eisei, and Taiho Pharmaceuticals.

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Document Review Tool

Number and title of document under review	2-29 (Version 2) Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection
Current Report Date	September 8, 2015
Clinical Expert	Dr. Brandon Meyers
Research Coordinator	Lisa Durocher-Allen
Assessment Date	November 23, 2017
Approval Date and Review Outcome (once completed)	September 25, 2019 ENDORSE

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes with modifications

Review Outcome as recommended by the Clinical Expert	ENDORSE
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	Not applicable
DSG/Expert Panel Commentary	Members of the DSG agreed with adding qualifying statements to 2 of the recommendations to highlight the newer evidence. It was also suggested to include mismatch repair deficiency together with microsatellite instability where the latter was mentioned in the recommendations.

Table 1. Summary of Relevant Guidelines

Citation (ref)	Search dates	Recommendations
Hellenic Society of Medical Oncology Kountourakis et al. 2016 [3]	Consensus Process; no lit search details	• For low risk stage II disease, single agent fluoropyrimidine could be considered, but the absolute risk reduction for recurrence is limited • High-risk stage II pts should be considered for adjuvant chemotherapy with single agent fluoropyrimidine or FOLFOX for a duration of 6 months. • Stage III patients should receive fluoropyrimidine and oxaliplatin-based adjuvant chemotherapy for a duration of 6 months • Whenever fl uoropyrimidine- and oxaliplatin-based combination is contraindicated, single agent fluoropyrimidine could be considered • Patients older than 70 years of age with high risk for recurrence could be considered for adjuvant chemotherapy with single agent fluoropyrimidine for 6 months. Although combination treatment with oxaliplatin is an option for stage III disease, it should be noted that the additional benefit conferred is questionable for this age group • For stage II patients MSI testing should be strongly considered as it can have a significant impact on prognosis and outcome • Infusional 5-FU should be preferred over bolus 5-FU • Oral capecitabine is an effective alternative to intravenous fluorouracil plus LV in the adjuvant treatment of colon cancer
American Society of Colon and Rectal Surgeons Vogel et al. 2017 [4]	January 1, 1997 – April 21, 2017 Medline, Embase, Cochrane Database of Collected Reviews	• Adjuvant chemotherapy is typically recommended for patients with stage III colon cancer. • First line adjuvant chemotherapy regiment for stage III colon cancer, in general, should include a fluoropyrimidine (5-FU/LV or capecitabine) and oxaplatin • Patients with high frequency MSI stage III colon cancer, fluorouracil-based chemotherapy had no benefits in terms of OS • Adjuvant chemotherapy may be considered for patients with high risk stage II colon cancer. • Most data suggest that there is minimal to no benefit to adjuvant treatment in patients with “good risk” stage II colon cancer.

Japanese Society for Cancer of the Colon and Rectum Watanabe et al. 2015 [5]	January 2008-March 2012 Pubmed, Ichushi-Web, English and Japanese articles	• Even for patients 70 years or older, postoperative adjuvant chemotherapy is recommended if their PS is good, if the function of their major organs is adequate, and if there are no complications that may be a risk for performing chemotherapy • The usefulness of postoperative adjuvant chemotherapy for Stage II has not been proved, it is recommended not to routinely administer adjuvant chemotherapy to all patients with Stage II. • Although no definitive conclusion regarding the duration of postoperative adjuvant chemotherapy has been reached, the current standard duration of treatment by 5-FU based adjuvant chemotherapy is 6 months. • Recommended therapy (listed in the order of the date of their coverage by Japanese National Health Insurance: 5-FU + I-LV, UFT + LV, Cape, FOLFOX, CapeOX
Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Colorectal Cancer [6] The SCAN Colorectal Systemic Therapy Workgroup	ADAPTE process with 5 international PG (NCCN for colon and rectal cancer, ESMO for advanced and early cancer and NICE)	• Pts with low risk stage II disease can be enrolled in a clinical trial, observed without adjuvant therapy, or considered for capecitabine or 5-FU/leucovorin (LV). The addition of oxaliplatin to 5-FU-based therapy is not considered appropriate adjuvant therapy in patients with stage II disease without high risk features. • Pts with high risk stage II disease can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx), or bolus 5-FU/LV/oxaliplatin (FLOX). Observation without adjuvant therapy is also an option in this population. • The panel recommends that mismatch repair (MMR) testing be considered to assist decision-making in patients with stage II disease. • For pts with stage III disease, the panel recommends 6 months of adjuvant chemotherapy after primary surgical treatment. Treatment options: FOLFOX (preferred), CAPEOX (preferred) FLOX or single agent capecitabine or 5-FU/LV in pts for whom oxaliplatin therapy is believed to be inappropriate • The panel cautions that a benefi t for the addition of oxaliplatin to 5-FU/LV in patients aged 70 years and older has not been proven in stage II or stage III colon cancer. Individualised assessment will assist in decision-making for older patients with CRC. • The panel recommends against the use of bevacizumab, cetuximab, panitumumab, or irinotecan in adjuvant therapy for non-metastatic disease

Cape: capecitabine; CapeOX: capecitabine/oxaliplatin; Flox: fluorouracil/leucovorin/oxaliplatin; FOLFOX: fluorouracil, leucovorin, and oxaliplatin; FU: fluorouracil; LV: leucovorin; MMR: mismatch repair; MSI: microsatellite instability; OS: overall survival; PS: performance status; UFT: uracil/tegafur

Table 2. Summary of Relevant Systematic Reviews

Citation (ref)	Search details	Inclusion criteria	Intervention/comparison	Results	Included studies
Cochrane Collaboration Chionh et al. 2017 [7]	Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 5), MEDLINE, Embase, Web of Science	RCT comparing oral and IV fluoropyrimidine chemo in pts treated with curative or palliative intent in CRC. * Only curative data shown.	Oral vs IV fluoropyrimidine	• DFS did not differ between participants treated with oral versus IV (HR= 0.93, 95% CI 0.87 to 1.00; 7 studies, 8903 pts; moderate-quality evidence). • OS did not differ between participants treated with oral versus IV (HR 0.92, 95%CI 0.84 to 1.00; 7 studies, 8902 pts; high-quality evidence). • Grade ≥ 3 AEs: Participants treated with oral experienced less grade ≥ 3 neutropenia/granulocytopenia (OR) 0.14, 95% CI 0.11 to 0.16; seven studies, 8087 pts; moderate-quality evidence), stomatitis (OR 0.21, 95% CI 0.14 to 0.30; five studies, 4212 pts; low-quality evidence), and any grade ≥ 3 AEs (OR 0.82, 95% CI 0.74 to 0.90; 5 studies, 7741 pts; low-quality evidence). There was more grade ≥ 3 hand foot syndrome (OR 4.59, 95% CI 2.97 to 7.10; five studies, 5731 pts; low-quality evidence) in patients treated with oral. No differences between pts treated with oral vs IV in occurrence of grade ≥ 3 diarrhea (OR 1.12, 95% CI 0.99 to 1.25; 9 studies, 9551 pts; very low-quality evidence), febrile neutropenia (OR 0.59, 95% CI 0.18 to 1.90; 4 studies, 2925 pts; low-quality evidence), vomiting (OR 1.05, 95% CI 0.83 to 1.34; 8 studies, 9385 participants; low-quality evidence), nausea (OR 1.21, 95% CI 0.97 to 1.51; 7 studies, 9233 participants; low-quality evidence)	Allegra 2015 De la Torre 2008 Hofheinz 2012 Kim 2001 De Gramont 2012 Lembersky 2006 Shimada 2014 Twelves 2012 Pectasides 2015

AE: adverse event; CI: confidence interval; CRC: colorectal cancer; DFS: disease-free survival; IV: intravenous; OR: odds ratio; OS: overall survival

Table 3. Summary of Relevant Primary Studies

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
Fluoropyrimidine + oxaplatin vs fluoropyrimidine					
Andre et al. 2015 MOSAIC [8]	Pts 18-75 yrs with resected stage II to III colon cancer	5-FU/LV arm(n=1123): LV, 2-hr infusion, 200 mg/m2, then 5-FU, IV bolus, 400 mg/m2 and 5-FU, 22-hr infusion, 600 mg/m2, days 1-2, cycle repeated every 2 weeks, 12 cycles 5-FU/LV + oxaliplatin arm (n=1123): LV, 2-hr infusion, 200 mg/m2, then 5-FU, IV bolus, 400 mg/m2 and 5-FU, 22-hr infusion, 600 mg/m2, days 1-2, cycle repeated every 2 weeks, 12 cycles. Oxaliplatin, 2-hr infusion, 85 mg/m2 day 1, given simultaneously with LV. **Also data below in effects of CT in those aged ≤70 vs >70 yrs old*	DFS, OS	9.46 years	Overall (LV5FU2 vs FOLFOX4), % (SE) 10 yrs DFS = 61.7 (1.6) vs 67.5 (1.5) HR = 0.82 (95% CI 0.71-0.95), p=0.007 10 yrs OS = 67.1 (1.6) vs 71.7 (1.5) HR = 0.85 (95%CI 0.73-0.99), p=0.043 Stage II 10 yrs DFS 73.6 (2.2) vs 75.2 (2.3) HR= 0.89, CI 0.68 to 1.16, p= .390 10 yrs OS 79.5 (2.2) vs 78.4 (2.2) HR = 1.00, CI 0.74-1.35, p=0.980 Stage III 10 yrs DFS 53.8 (2.1) vs 62.2 (2.0) HR= 0.79, CI 0.67-0.94, p=0.007 10 yrs OS 59.0 (2.1) vs 67.1 (2.0) HR= 0.80, CI 0.66-0.96, p =0.016
Schmoll et al. 2015 [9] NO16968, 29 countries	Pts 18 yrs or older with stage III resected colon cancer between April 2003-October 2004	XELOX : 2-hour iv infusion of oxaliplatin 130mg/m^2 on d1 and outpatient oral capecitabine 1,000 mg/m^2 twice daily on d1-14 of a 3-week cycle for a total of eight cycles.	DFS, OS	74 mths	Xelox vs FU/FA DFS: HR 0.80, 95% CI, 0.69 to 0.93; P= .004 After 3 to 7 years of follow-up, the DFS rates were consistently higher in the XELOX group than in the FU/FA

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		FU/FA regimens from The MayoClinic of 24weeks, six cycles and from Roswell Park of 32weeks, four cycles were given as described previously. The FU/FA regimen was prespecified at each participating center before the study started.			group; rates were 71% versus 67% (year 3), 69% versus 62% (year 4), 67% versus 61% (year 5), 66% versus 58% (year 6), and 63% versus 56% (year 7). OS: HR 0.83; 95%CI 0.70-0.99, p=.04 After 3 to 7 years of follow-up, the OS rates were consistently higher in the XELOX group than in the FU/FA group; rates were 86% versus 84% (year 3), 80% versus 78% (year 4), 77% versus 74% (year 5), 76% versus 71% (year 6), and 73% versus 67% (year 7).
Shah et al. 2016 [10] ACCENT Pooled analysis	Pooled analysis of mature outcome data of 3 contemporary RCT: MOSAIC, C-07, XELOXA (n = 6,468)	FOLFOX vs FU + LV	Risk of recurrence, death	6 years	The addition of oxaliplatin: - diminished the risk of recurrence over time to a greater degree, more uniformly over time and for a longer period of time for patients with stage III disease. Higher risk of recurrence over time was associated with higher nodal stage with oxaliplatin demonstrating more benefit in patients with more advanced nodal stage disease. - associated with benefit for patients with both T3 and T4 stage tumors; however, little benefit is evident for patients with T1 and T2 stage tumors - reduced the recurrence risk over time for both low- and high-grade tumors for the first 5 years posttreatment - reduces the time-dependent hazard of death from 1.5 years to 6 years post

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
					treatment. Stage II disease did not show a significant reduction at any time point. - does not impact the risk of early death (OR, 0.98; 95% CI, 0.82 to 1.18; P = .86), but does decrease the risk of mid deaths by 16% (OR, 0.84; 95% CI, 0.71 to 0.99; P = .04) and late deaths by 20%(HR, 0.80; 95% CI, 0.67 to 0.95; P =.01)
a) Duration (3 vs 6 months)					
Andre et al. 2017 [11] *Abstract* IDEA France	PTs with stage III colon cancer undergoing mFOLFOX6 or XELOX between May 2009 and May 2014 (n= 2,022)	3 mths vs 6 mths of chemotherapy with mFOLFOX6 or XELOX (physician/pts choice).	DFS	50.2 mths	mFOLFOX6: 90% and XELOX 10% of pts 3 yr DFS Overall : 72.1% 3M vs. 75.7% 6M (HR=1.24; 95%CI 1.05-1.46, p=0.0112) mFOLFOX6: 72.0% 3M vs. 76.3% 6M (HR=1.27; 95%CI 1.07-1.51 p=0.0069) overall maximal neuropathy grade 0-1/2/3-4 was 63.6/28.5/7.9% in 3M and 33.4/41.3/25.3% in 6M; p<0.0001 * with 90% of patients treated with mFOLFOX6 regimen has shown that 6 months adjuvant treatment is superior to 3 months treatment
Grothey et al. 2018 [1] *Pooled analysis of 6 RCT, phase III (CALGB/SWOG*	Pts with stage III colon cancer undergoing FOLFOX or CAPOX therapy between	3 months (n =3870) vs 6 months (n=3893)	DFS, Adverse events	41.8 mths	DFS at 3 years All pts: 3M 74.6% (CI 73.5-75.7) vs 6M 75.5% (CI 74.4-76.7); HR= 1.07 (95%CI 1.00-1.15, p=0.11) for non inferiority of 3M; p=0.045 for superiority of 6M

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
80702 [NCT01150045}, IDEA France, SCOT, ACHIEVE, TOSCA, HORG)	June 2007-December 2015 (N=12,834) *5 of the 6 trials allowed use of either FOLFOX4 or modified FOLFOX6. *Overall 40% used CAPOX and 60% used FOLFOX.				FOLFOX pts: 3M 73.6% vs 6M 76.0%, HR = 1.16 (CI 1.06-1.26), p=0.001 CAPOX pts: 3M =75.9% vs 6M = 74.8%, HR = 0.95 (CI 0.85-1.06) Low risk cancer: 3M 83.1% vs 6M 83.3%, HR =1.01 (CI .90-1.12) High risk cancer: 3M 62.7% vs 6M 64.4%, HR 1.12 (CI 1.03-1.23, p= 0.01) Any adverse event (3M vs 6M) FOLFOX, p <0.001, Grade 1 (30.7 vs 11.0), Grade 2 (31.6 vs 32.1), Grade 3 or 4 (37.6 vs 56.9) CAPOX, p <0.001, Grade 1 (35.0 vs 14.6), Grade 2 (40.8 vs 48.5), Grade 3 or 4 (24.2 vs 36.9)
Iveson et al. 2018 [12] *SCOT Study*; UK, Australia, Spain, Sweden, Denmark, New Zealand	Pts aged 18 yrs or older with high-risk stage II and III who underwent curative resection between March 27 2008 and Nov 29 2013	3 months (n=3044) vs 6 months (n=3044) of FOLFOX or CAPOX FOLFOX: every 2 weeks; oxaliplatin IV 85 mg/m^2 over 2 hrs D1 concurrently with L-folinic acid 175 mg or folinic acid (leucovorin) 350 mg. IV bolus injection of fluorouracil 400 mg/m^2 over 5 min, then a continuous IV fluorouracil 2400 mg/m^2 over 46 h. 6 cycles for 3 mths group and 12 cycles for 6 mths group.	DFS Adverse events	Median F/U 37 months	3 yrs DFS (3 mths vs 6 mths) All: 76·7% (95% CI 75·1–78·2) vs 77·1% (75·6–78·6) HR= 1·006 (0·909–1·114, p=0·012) FOLFOX: 76·3% (73·5 to 79·0) vs 79·2% (76·6 to 81·8), HR = 1·158 (0·964–1·391) CAPOX: 76·9% (75·0 to 78·7) vs 76·1% (74·2 to 78·0) HR 0·944 (0·835–1·067) The frequency of grade 3–5 diarrhoea (p=0·033), neutropenia (p=0·031), pain (p=0·014), hand-foot syndrome (p=0·031), and sensory neuropathy

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		CAPOX: every 3 weeks; IV oxaliplatin 130 mg/m^2 D1over 2 h. Oral capecitabine 1000 mg/m^2 2x per day/first 14 days each cycle. Pts with creatinine clearance of 30–50 mL/min had to start treatment with capecitabine at 75% of the full dose. 4 cycles 3 mth group or 8 cycles 6 mth group			(p<0·0001) was significantly higher in the 6 month group than in the 3 month group.
Lonardi et al. 2016 [13] TOSCA trial	Open-label, phase III, multicenter, noninferiority trial randomizing patients with high-risk stage II or stage III radically resected colon cancer between June 2007 to March 2013 to receive 3 months (arm 3 m) versus 6 months (arm 6 m) of FOLFOX4/XELOX	3 mths (n=1839) vs 6 mths (n = 1858) of FOLFOX-4 or XELOX FOLFOX-4 : IV OXA 85 mg/m2 over 2 h, concurrently with LV 100 mg/m^2, followed by 5-FU 400 mg/m^2 as bolus injection and 5-FU 600 mg/m^2 as IV over 22 h on D1. On D2, LV 100 mg/m^2, 5-FU400 mg/m2 bolus injection, and 5-FU 600 mg/m2 IV over 22 h were administered as previous day. Cycles were repeated every 14 days for a total of 6 cycles in arm 3 m or 12 cycles in arm 6 m. XELOX : IV OXA 130mg/m^2 over 2 h on day 1, followed by capecitabine (CAPE) 1000mg/m^2 per os twice	Adverse events	ongoing	Treatment was permanently discontinued in 8% of patients in arm 3 m vs 33% in arm 6 m. Reasons for treatment permanent discontinuation were toxicity or AE in 6% of patients in arm 3 m versus 20% of those in arm 6 m (P < 0.001). Eighty-nine percent of patients in arm 6 m received a minimum of 3 months of treatment (proportion almost identical to that of patients in arm 3 m). Grade 3+ toxicities were higher in arm 6 m versus arm 3 m: neutropenia (27.6% versus 20.7%, P< 0.0001), diarrhea (6.4% versus 5.0%, P< 0.0001) and allergic reactions (2.0% versus 0.5% P< 0.0001). As expected, Grade 2+ neuropathy was higher in arm 6 m compared with arm 3 m (grade 2, 22.8% versus 7.5%, respectively; grade 3, 8.2% versus 1.1%, respectively; and grade 4, <1% each, P< 0.0001)

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
Labianca et al. 2017 [14] TOSCA trial		daily on day 1–14. Cycles were repeated every 21 days for a total of 4 cycles in arm 3 m or eight cycles in arm 6 m.	Relapse free survival	Median f/u 62 months	8 yr RFS 75%, OS 80% HR 3 mths vs 6 mths for relapse/death = 1.14 (95%CI 0.99-1.31, p for non-inferiority=0.506) HR for survival= 1.07 (95%CI 0.89-1.29, p for non-inf.=0.249) * TOSCA was not able to demonstrate that 3 months of oxaliplatin-based adjuvant treatment is as efficacious as 6 months
Yoshino et al. 2017 [15] *Abstract* ACHIEVE trial, Japan	Stage III pts to receive 3m or 6m of mFOLFOX6/CAPOX after surgery between 2012 and 2014 (n= 1291)		DFS, neurotoxicity	39mths	Neurotoxicity (=>grade 3)= 3 mths 1% vs 6 mths 6%, p<0.001) 3-year DFS rate: Overall: 3 mths 79.5% and 6 mths 77.9% for 6m HR= 0.954, 95%CI, 0.758-1.201 low risk (T1-3 and N1) = HR= 0.811 (0.532-1.236) and high-risk (T4 or N2)= 1.066 (0.810-1.403) FOLFOX = HR= 1.065 (0.709-1.600) CAPOX= 0.904 (0.684-1.195)
Effects of CT in those aged ≤70 vs >70 yrs old					
Andre et al. 2015 [8] MOSAIC	Pts 18-75 yrs with resected stage II to III colon cancer	LV5FU2 vs FOLFOX4	OS	9.46 years	≤70 yrs: HR =0.78 (0.66-0.93), p =0.006 > 70 yrs: HR = 1.19 (0.83-1.7), p= 0.338

AE: adverse event; CAPOX: capecitabine and oxaliplatin; CI: confidence interval; CT: ; D1: day 1; DFS: disease-free survival; f/u: follow up; FA: folinic acid; FOLFOX: fluorouracil, leucovorin, and oxaliplatin; FU: fluorouracil; HR: hazard ratio; IV: intravenous; LV: leucovorin; M, mths: months; MOSAIC: Adjuvant Treatment of Colon Cancer; OS: overall survival; OXA: oxaliplatin; Pts: patients;

RCT: randomized controlled trial; RFS: relapse-free survival; TOSCA: Three or Six Colon Adjuvant; XELOX: capecitabine plus oxaliplatin; XELOXA: adjuvant XELOX; yr(s): year(s)

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Appendix 1. Members of the Expert Panel

Name	Centre	Conflict of Interest Declaration
Jim Biagi	Kingston	None declared
Charles Cho	Southlake, Newmarket	None declared
Mark Doherty	Odette, Toronto	None declared
Valerie Francescutti	Hamilton	Owner of an incorporated medical professional practice
Robert Gryfe	Mt. Sinai, Toronto	None declared
Julie Hallet	Odette, Toronto	Received honoraria from Novartis Oncology and Ipsen Biopharmaceuticals Canada for speaking at institutional rounds across Ontario. This was not a speaker bureau. The companies had no influence on the content of the slides or the talks. Unrestricted research grant from Canada Health Infoway: $50,000.00 Unrestricted educational grant from Baxter Corporation: $3,000.00
Nazik Hammad	Kingston	None declared
Khalid Hirmiz	Windsor	None declared
Maria Kalyvas	Kingston	None declared
Paul Karanicolas	Odette, Toronto	Received $500 or more in a single year for research support from Sanofi and Baxter
Erin Kennedy	Mt. Sinai, Toronto	Principal investigator for Canadian Partnership Against Cancer Rectal Cancer Project 2014-2017 Non-operative management for locally advanced low rectal cancer CIHR 2016-2021
Fayez Quereshy	Princess Margaret, Toronto Western, Toronto	Received $500 or more in a single year to act in a consulting capacity offering educational lectures for industry partners in Medtronic, Ethicon, and Minogue Medical
Jolie Ringash	Princess Margaret, Toronto	None declared
Mark Rother	Peel, Mississauga	None declared
Raimond Wong	Hamilton	None declared

Appendix 2. Search Strategy

1	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treple$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
2	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or metaanalysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.
3	practice guidelines/ or practice guideline?.tw. or practice guideline.pt.
4	2 not 1
5	3 not (1 or 2)
6	exp colon tumor/ or exp colorectal neoplasms/ or (((colon or colonic or colorectal) adj (cancer: or tumor: or tumour: or neoplasm:)) or cancer of the colon).mp.
7	adjuvant chemotherapy/ or (chemotherapy and adjuvant).mp. or (chemotherapy or systemic therapy).tw.
8	6 and 7
9	8 and ((201508: or 201509: or 20151: or 2016: or 2017: or 2018:).ed. or (201508: or 201509: or 20151: or 2016: or 2017: or 2018:).dd. or (201508: or 201509: or 20151: or 2016: or 2017: or 2018:).em.)
10	1 and 9
11	4 and 9
12	5 and 9
13	remove duplicates from 10
14	remove duplicates from 11
15	remove duplicates from 12
16	limit 13 to english
17	limit 14 to english
18	limit 15 to english

DEFINITIONS OF REVIEW OUTCOMES

4. **ARCHIVE – A**RCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

5. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

6. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.