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Guideline 2-29 Version 4 IN REVIEW

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

An assessment conducted in December 2025 placed Guideline 2-29 Version 4 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

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)**
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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

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.