Guideline 2-29 Version 2 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

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An assessment conducted in November 2017 placed Evidence-based Series (EBS) 2-29 Version 2 IN REVIEW. This means 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)

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

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.

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 FOLFOX for high-risk patients as part of an informed discussion between patients and their medical oncologists regarding treatment options.
Recommendation 3
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 stage II (in the absence of high-risk features) where a patient does not require adjuvant chemotherapy, MSI 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 status (a low risk factor), the choice of treatment is between observation and FOLFOX, 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:
- FOLFOX or FLOX or XELOX
- 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 XELOX. 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.

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.