

# Early Stage Colon Cancer

Effective Date: May 2023



## Background

In 2022, it is estimated that in Canada, 24300 people will develop colorectal cancer (13500 males and 10800 females).<sup>1</sup>

A patient may be predisposed to develop colorectal cancer by a hereditary condition (e.g.: hereditary non-polyposis colon cancer, familial adenomatous polyposis) or a personal history of either inflammatory bowel disease (e.g.: Crohn’s disease, ulcerative colitis) or adenomatous polyps. Over 60 percent of colorectal cancers are without a clearly identifiable predisposing factor, however.

In the absence of hereditary cancer syndromes, the progression from adenoma to adenocarcinoma occurs sporadically as a result of acquired genetic alterations. Allelic loss, chromosomal amplifications, or translocations account for 85 percent of such cases. In the other 15 percent, epigenetic silencing of a component of the DNA mismatch repair system allows frame-shift mutations and base-pair substitutions to persist. The resultant accumulation of tandemly repeated nucleotide sequences (“microsatellites”) facilitate further changes during replication (“genetic instability”). While most microsatellites fail to occur within regulatory genes, microsatellites within critical coding regions of genes involved in the regulation of cell growth predispose to loss of function of a tumor suppressor genes or to the gain of function of an oncogene.

Patients with tumours that display “high-frequency microsatellite instability” achieve a better five-year overall survival than patients with tumours that display microsatellite stability or low-frequency instability (HR 0.31, CI<sub>95%</sub> 0.14-0.72,  $p = 0.004$ ).<sup>2</sup> The use of adjuvant 5-Fluorouracil and Leucovorin chemotherapy fails to improve overall survival in patients with tumours that display high-frequency microsatellite instability (HR 1.07, CI<sub>95%</sub> 0.62-1.86,  $p = 0.80$ ).

After a diagnosis of colorectal cancer, prognosis depends upon the stage at diagnosis; that is, prognosis is better with less penetration of tumour into the bowel wall, fewer involved regional lymph nodes, and no evidence of metastatic disease.

Because the prognosis is better when colorectal cancer is identified at an earlier stage, because of the relatively high incidence of colorectal cancer, and because of the simplicity and accuracy of screening tests, screening for colorectal cancer represents an important component of routine care for all adults aged fifty years or older. This is especially important in patients with first-degree relatives with colorectal cancer.

## Guideline Questions

1. What are the recommendations for the diagnostic workup of adult patients with potentially resectable colon cancer?
2. What are the recommendations for adjuvant chemotherapy in adult patients with colon cancer resected with curative intent and without evidence of metastatic disease?

## Search Strategy

This guideline was developed to promote evidence-based practice in Alberta. It was compiled from the results of randomized controlled trials and systematic reviews, derived from an English language and relevant term search of PubMed and MEDLINE from 1990 forward. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team's interpretation of the data. For the 2023 update of this guideline, recommendations were modified based on a consensus discussion at the 2023 Annual Gastrointestinal Tumour Team Meeting. However, no formal update of the literature was performed.

## Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with early stage colon cancer. Different principles may apply to pediatric patients.

## Recommendations and Discussion

### Suggested Diagnostic Work-Up

- Prior to an attempt at resection of an intraluminal mass, it is recommended that, in the absence of a complete bowel obstruction, a colonoscopy be completed to exclude synchronous neoplasms.
- A CT scan of the thorax, abdomen, and pelvis is recommended to exclude the possibility of metastatic disease and to provide a baseline for the surveillance CT scans. To evaluate an abnormality identified on CT scan, further imaging (e.g.: MR, ultrasound) may be required.
- A pre-operative CEA is recommended for future comparison. A post-operative CEA should be requested to ensure that it has normalized if it was elevated before surgery. ASCO recommends tumour budding should be assessed pre-operatively as well, however, at this time we believe the evidence is not strong enough to recommend adjuvant chemotherapy solely based on high levels of tumour budding.<sup>3</sup>
- The number of risk factors should be considered as part of the shared decision-making process. The presence of more than one risk factor may increase the risk of recurrence.<sup>4</sup>

### Stage Information

**Table 1.** AJCC Cancer Staging System for Early Stage Colon Cancer, 8th Edition.

Stage	Depth of Tumour Penetration		Regional Lymph Node Involvement		Metastases	
Stage 0	T <sub>is</sub>	Carcinoma <i>in situ</i>	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage I	T <sub>1</sub>	Invasion into submucosa	N <sub>0</sub>	None	M <sub>0</sub>	Absent
	T <sub>2</sub>	Invasion into muscularis propria	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage II <sub>A</sub>	T <sub>3</sub>	Invasion through muscularis propria into peri-colic tissues	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage II <sub>B</sub>	T <sub>4a</sub>	Tumor invades through the visceral peritoneum	N <sub>0</sub>	None	M <sub>0</sub>	Absent

Stage	Depth of Tumour Penetration		Regional Lymph Node Involvement		Metastases	
Stage II <sub>c</sub>	T <sub>4b</sub>	Direct invasion into, or adherence <sup>§</sup> to, other structures	N <sub>0</sub>	None	M <sub>0</sub>	Absent
Stage III <sub>A</sub>	T <sub>1-2</sub>	As described above	N <sub>1</sub>	One to three lymph nodes	M <sub>0</sub>	Absent
			N <sub>1c</sub>	Tumour deposits in subserosa, mesentery, or peri-rectal tissues		
	T <sub>1</sub>	Invasion into submucosa	N <sub>2a</sub>	Four to six lymph nodes	M <sub>0</sub>	Absent
Stage III <sub>B</sub>	T <sub>3-4a</sub>	As described above	N <sub>1</sub>	One to three lymph nodes	M <sub>0</sub>	Absent
			N <sub>1c</sub>	As described above		
	T <sub>2-3</sub>	As described above	N <sub>2a</sub>	As described above	M <sub>0</sub>	Absent
	T <sub>1-2</sub>	As described above	N <sub>2b</sub>	Seven or more lymph nodes	M <sub>0</sub>	Absent
Stage III <sub>C</sub>	T <sub>4a</sub>	Penetration to surface of visceral peritoneum	N <sub>2a</sub>	As described above	M <sub>0</sub>	Absent
	T <sub>3-4a</sub>	As described above	N <sub>2b</sub>	As described above	M <sub>0</sub>	Absent
	T <sub>4b</sub>	Direct invasion into, or adherence <sup>§</sup> to, other structures	N <sub>1-2</sub>	As described above	M <sub>0</sub>	Absent
Stage IV <sub>A</sub>	T <sub>any</sub>	As described above	N <sub>any</sub>	As described above	M <sub>1a</sub>	One site*
Stage IV <sub>B</sub>	T <sub>any</sub>	As described above	N <sub>any</sub>	As described above	M <sub>1b</sub>	Multiple sites*
Stage IV <sub>C</sub>	T <sub>any</sub>	As described above	N <sub>any</sub>	As described above	M <sub>1c</sub>	Metastasis involving peritoneal surface

\* M<sub>1a</sub> refers to metastasis confined to one site (e.g.: liver, lung, ovary, non-regional lymph node) whereas M<sub>1b</sub> refers to metastasis in more than one site or within the peritoneum excluding the peritoneal surface.

<sup>§</sup> If the microscopic assessment identifies no tumor in the adhesion, classify based on anatomic depth of wall invasion.

**Note:** A peri-tumoural nodule in the peri-colic adipose tissue without histologic evidence of lymph node architecture may represent discontinuous spread, venous invasion with extravascular spread, or a totally replaced lymph node.

## Goal of Therapy

To render the patient free of disease and to delay or prevent recurrence.

## Recommendations

1. After surgical resection of the tumour, the patient's need for adjuvant chemotherapy should be defined based upon the stage and the medical oncologist's assessment of the patient's relevant comorbidities (e.g.: diabetes mellitus, hypertension, cardiac status, etc.). The presence of at least one high-risk feature should prompt consideration for systemic adjuvant chemotherapy in stage II disease.
2. Ideally, adjuvant chemotherapy should be initiated as soon as possible (once the patient has recovered from surgery).<sup>5</sup> If this is not possible due to post-operative complications, adjuvant chemotherapy could still be considered up to twelve weeks after surgery.
3. Consider treatment on a clinical trial, if available.
4. To optimize the care of patients with resected colon cancer, the patient's case should be reviewed with the multidisciplinary team.

**Table 2.** Recommendations for Adjuvant Treatment of Early Stage Colon Cancer.

Stage	Recommendations
<b>Stage 0</b>	<ul style="list-style-type: none"> <li>• Although stage 0 disease is typically identified incidentally at the time of a colonoscopic polypectomy, inadequate margins warrants further endoscopic or surgical resection with oncologic principles.</li> <li>• No adjuvant systemic therapy is indicated.</li> </ul>
<b>Stage I</b>	<ul style="list-style-type: none"> <li>• Perform surgical resection with oncologic principles.<sup>6, 7</sup></li> <li>• No adjuvant systemic therapy is indicated.</li> </ul>
<b>Stage II</b>	<ul style="list-style-type: none"> <li>• Perform surgical resection with oncologic principles.</li> <li>• Adjuvant chemotherapy should not routinely be offered to patients who are at low risk for recurrence, including:<sup>8-11</sup> [Level of Evidence: IV; Strength of Recommendation: C] <ul style="list-style-type: none"> <li>• Stage IIA (T3) tumours with at least 12 sampled lymph nodes</li> <li>• Absence of perineural or lymphovascular invasion, poor or undifferentiated tumour grade, clinical intestinal obstruction, tumour perforation</li> <li>• Less than grade BD3 tumour budding</li> </ul> </li> <li>• If a “high-risk” or “poor prognosis feature” is present, consider adjuvant chemotherapy as for stage III disease. However, the benefit of Oxaliplatin in stage II disease has been questioned.<sup>12-15</sup></li> <li>• “High-risk” features include direct invasion into adjacent structures, perforation through the tumor, clinical obstruction at presentation, poorly-differentiated histology, lymphovascular and/or perineural invasion, or evaluation of less than twelve regional lymph nodes.</li> <li>• All patients with high risk stage II disease should be tested for microsatellite instability to guide the choice of adjuvant chemotherapy. If present, referral to the Genetics Counseling Service should be considered. Systematic reviews have suggested that high levels of microsatellite instability confer a better overall survival as well as a possible resistance to 5-Fluorouracil.<sup>2, 16, 17</sup></li> <li>• For patients with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI) tumours: <ul style="list-style-type: none"> <li>• Adjuvant fluoropyrimidine-only chemotherapy is not routinely recommended [Level of Evidence: IV; Strength of Recommendation: C]</li> <li>• Poor differentiation is not considered a high-risk prognostic factor in patients with dMMR or MSI tumours</li> <li>• For patients with dMMR or MSI and T4 tumours and/or other high-risk features (with the exception of poor differentiation), oxaliplatin-containing chemotherapy may be considered. There is no compelling evidence to suggest that age of patient should alter this recommendation. Specifically, there is no evidence that younger low-risk stage II patients should be offered ACT on the basis of their age alone.</li> <li>• Patients with proficient mismatch repair/microsatellite stable (pMMR or MSS) tumours are included within the previously mentioned recommendations (see "high risk features above").</li> </ul> </li> <li>• Circulating tumor DNA (ctDNA) was identified as an emerging potential predictive factor; however, there is insufficient evidence regarding the predictive value of chemotherapy</li> </ul>
<b>Stage III</b>	<ul style="list-style-type: none"> <li>• Perform surgical resection with oncologic principles.</li> <li>• When compared to no adjuvant chemotherapy therapy, 5-Fluorouracil-based regimens</li> </ul>

Stage	Recommendations						
	<p>reduce the relative risk of death by 30 to 36%.<sup>17-19</sup></p> <ul style="list-style-type: none"> <li>Adjuvant chemotherapy options include:</li> </ul> <table border="1" data-bbox="277 304 1479 1115"> <tr> <td data-bbox="277 304 516 653">CAPOX/ XELOX<sup>20</sup></td> <td data-bbox="516 304 1479 653">Refer to <a href="#">“Capecitabine: A Guide for Patient Care.”</a> NO16968 demonstrated an improvement in both the disease-free survival (66.1% <i>versus</i> 59.8%, HR 0.80, CI<sub>95%</sub> 0.69-0.93, <i>p</i> = 0.0045) and relapse-free survival (67.8% <i>versus</i> 60.9%, HR 0.78, CI<sub>95%</sub> 0.67-0.92, <i>p</i> = 0.0024) when compared 5-Fluorouracil and Leucovorin by either the Mayo or Roswell Park regimens. Although overall survival was not statistically significantly superior (77.6% <i>versus</i> 74.2%, HR 0.87, CI<sub>95%</sub> 0.72-1.05, <i>p</i> = 0.1486), the Kaplan-Meier curves continue to separate.</td> </tr> <tr> <td data-bbox="277 653 516 1001">Modified FOLFOX<sup>12, 21</sup></td> <td data-bbox="516 653 1479 1001">This regimen requires placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port. For the subset of patients with stage III disease, the MOSAIC trial suggested that the addition of Oxaliplatin to 5-Fluorouracil and Leucovorin improves five-year disease-free (66.4% <i>versus</i> 58.9%, HR 0.78, CI<sub>95%</sub> 0.65-0.93, <i>p</i> = 0.005) and six-year overall survival (72.9% <i>versus</i> 68.7%, HR 0.80, CI<sub>95%</sub> 0.65-0.97, <i>p</i> = 0.023). The benefit of Oxaliplatin in patients over seventy years of age has been questioned.<sup>10-12,20</sup></td> </tr> <tr> <td data-bbox="277 1001 516 1115">Capecitabine<sup>22</sup></td> <td data-bbox="516 1001 1479 1115">Refer to <a href="#">“Capecitabine: A Guide for Patient Care.”</a> Capecitabine has been shown to be equally efficacious as, but less toxic and less resource intensive than, the “Mayo Regimen” (see below).</td> </tr> </table> <p>The optimal duration of Oxaliplatin-based adjuvant chemotherapy (CAPOX or FOLFOX) is 6 months. Based on the primary analysis of the IDEA collaboration, the non-inferiority of 3 months is not proven (HR1.07 95% CI 1.00-1.15) using a non-inferiority margin 1.12.<sup>23</sup> However, given the cumulative-dose dependent toxicity of oxaliplatin,<sup>24</sup> a duration of 3 months may be considered in select patients after an informed discussion about the relative risks and benefits (Shi, JCO, 2017). Based on sub-group analyses from the IDEA collaboration, both regimen and risk group can be considered, though not randomized (regimen and risk group) or pre-planned (risk group) (Shi, JCO, 2017).</p> <ol style="list-style-type: none"> <li>1. Patients with low risk stage III disease (T1-3,N1) who are fit enough to tolerate CAPOX, do not have inferior outcomes with 3 compared to 6 months of adjuvant chemotherapy (HR 0.85 95% CI 0.1-1.01). Not all patients may be eligible for CAPOX and if FOLFOX is a preferred regimen, 6 months remains standard (HR1.10, 95% CI 0.96-1.26).</li> <li>2. For patients with high risk disease (T4 or N2), 6 months of either CAPOX (HR1.02, 95% CI 0.89-1.17) or FOLFOX remains standard. 3 months of FOLFOX in particular was clearly inferior to 6 months and should not be offered (HR1.16, 95% CI1.06-1.26).</li> </ol> <p>Other regimens may be considered in specific clinical situations:</p> <ol style="list-style-type: none"> <li>1. Mayo Regimen:<sup>25, 26</sup> Six four-week cycles where Leucovorin 20 mg/m<sup>2</sup> IV</li> </ol>	CAPOX/ XELOX <sup>20</sup>	Refer to <a href="#">“Capecitabine: A Guide for Patient Care.”</a> NO16968 demonstrated an improvement in both the disease-free survival (66.1% <i>versus</i> 59.8%, HR 0.80, CI <sub>95%</sub> 0.69-0.93, <i>p</i> = 0.0045) and relapse-free survival (67.8% <i>versus</i> 60.9%, HR 0.78, CI <sub>95%</sub> 0.67-0.92, <i>p</i> = 0.0024) when compared 5-Fluorouracil and Leucovorin by either the Mayo or Roswell Park regimens. Although overall survival was not statistically significantly superior (77.6% <i>versus</i> 74.2%, HR 0.87, CI <sub>95%</sub> 0.72-1.05, <i>p</i> = 0.1486), the Kaplan-Meier curves continue to separate.	Modified FOLFOX <sup>12, 21</sup>	This regimen requires placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port. 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Stage	Recommendations
	<p>followed by 5-Fluorouracil 425 mg/m<sup>2</sup> IV are administered daily for five consecutive days.</p> <p>2. Roswell Park Regimen: Four eight-week cycles where Leucovorin (500 mg/m<sup>2</sup> IV over two hours) followed by 5-Fluorouracil (500 mg/m<sup>2</sup> IV bolus) are administered once every week for six weeks.</p>

5. As long as resection of either a metachronous polyp, colorectal cancer, or a metastasis to liver or lung remains appropriate, surveillance is recommended (see [Clinical Practice Guidelines for Colorectal Surveillance](#)).

## References

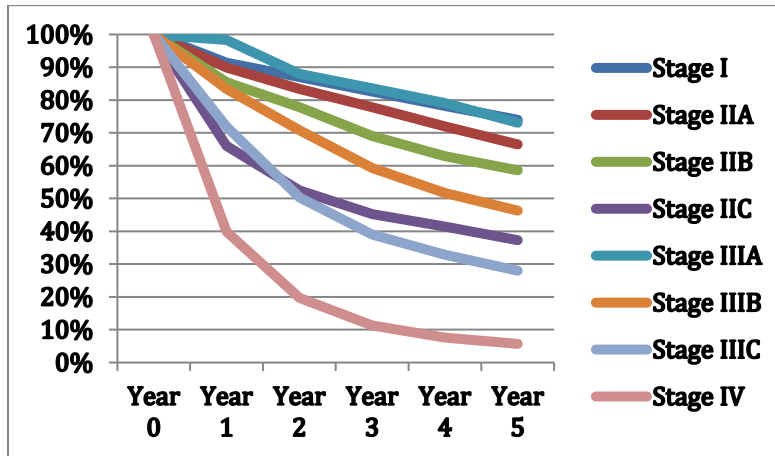
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## Appendix A:

**Figure 1.** Observed survival rates for 28,491 cases with adenocarcinoma of colon. Data from SEER 1973-2005.



## Appendix B: Chemotherapy Dosing and Schedule

Chemotherapy	Dose/Schedule
CAPOX/XELOX	Eight three-week cycles where Oxaliplatin 130 mg/m <sup>2</sup> is administered IV Q21d and Capecitabine 1,000 mg/m <sup>2</sup> is administered PO Q12h for fourteen days.
FOLFOX	Twelve two-week cycles where <ul style="list-style-type: none"> <li>· Oxaliplatin (85 mg/m<sup>2</sup> IV over two hours) and Leucovorin (400 mg/m<sup>2</sup> IV over two to six hours) are administered concurrently,</li> <li>· Followed by 5-Fluorouracil (400 mg/m<sup>2</sup> IV bolus),</li> <li>· Followed by a continuous intravenous infusion of 5-Fluorouracil (2,400 mg/m<sup>2</sup> over forty-six hours).</li> </ul>
Capecitabine	Eight three-week cycles where Capecitabine 1,250 mg/m <sup>2</sup> is administered PO Q12h for fourteen days.

## Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GI Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GI Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, gastroenterologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2008.

## Levels of Evidence

<b>I</b>	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
<b>II</b>	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
<b>III</b>	Prospective cohort studies
<b>IV</b>	Retrospective cohort studies or case-control studies
<b>V</b>	Studies without control group, case reports, expert opinion

## Strength of Recommendations

<b>A</b>	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
<b>B</b>	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
<b>C</b>	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
<b>D</b>	Moderate evidence against efficacy or for adverse outcome; generally not recommended
<b>E</b>	Strong evidence against efficacy or for adverse outcome; never recommended

## Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

AJCC, American Joint Committee on Cancer; CAPOX, capecitabine + oxaliplatin; CEA, carcinoembryonic antigen; CI, confidence interval; CT, computed tomography; CVC, central venous catheter; FOLFOX, oxaliplatin + leucovorin + 5-fluorouracil; HR, hazard ratio; IV, intravenous; MR, magnetic resonance; PET, positron emission tomography; PICC, peripherally inserted central catheter; PO, by mouth, orally; SEER, Surveillance, Epidemiology, and End Results database; TNM, tumour-node-metastasis; XELOX, oxaliplatin + capecitabine.

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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## Conflict of Interest Statements

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**Derek Tilley** has nothing to disclose.

\*Working group lead

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