

EARLY STAGE COLON CANCER

Effective Date: December 2017

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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.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Participation of members of the Alberta Provincial GI Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GI Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

BACKGROUND

According to statistics provided by the Canadian Cancer Society in 2013, one in thirteen Canadian males and one in fifteen Canadian females will be diagnosed with colorectal cancer in their lifetime.

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_{95%} 0.14-0.72, $p = 0.004$).¹ 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_{95%} 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

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

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists, gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge

Management Specialist from the Guideline Resource Unit. 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 February, 2008. This guideline was revised in August, 2009, March, 2010, June, 2011, October, 2013 and December 2017.

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 2017 update of this guideline, recommendations were modified based on a consensus discussion at the 2017 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.

Stage Information

Table 1. AJCC Cancer Staging System for Early Stage Colon Cancer, Seventh Edition.

Stage	Depth of Tumour Penetration		Regional Lymph Node Involvement		Metastases	
Stage 0	T _{is}	Carcinoma <i>in situ</i>	N ₀	None	M ₀	Absent
Stage I	T ₁	Invasion into submucosa	N ₀	None	M ₀	Absent
	T ₂	Invasion into muscularis propria	N ₀	None	M ₀	Absent
Stage II _A	T ₃	Invasion through muscularis propria into peri-colic tissues	N ₀	None	M ₀	Absent
Stage II _B	T _{4a}	Penetration to surface of visceral peritoneum	N ₀	None	M ₀	Absent
Stage II _C	T _{4b}	Direct invasion into, or adherence [§] to, other structures	N ₀	None	M ₀	Absent
Stage III _A	T ₁₋₂	As described above	N ₁	One to three lymph nodes	M ₀	Absent
			N _{1c}	Tumour deposits in subserosa, mesentery, or peri-rectal tissues		

Stage	Depth of Tumour Penetration		Regional Lymph Node Involvement		Metastases	
	T ₁	Invasion into submucosa	N _{2a}	Four to six lymph nodes	M ₀	Absent
Stage III _B	T _{3-4a}	As described above	N ₁	One to three lymph nodes	M ₀	Absent
			N _{1c}	Tumour deposits in subserosa, mesentery, or peri-colic tissues		
	T ₂₋₃	As described above	N _{2a}	Four to six lymph nodes	M ₀	Absent
	T ₁₋₂	As described above	N _{2b}	Seven or more lymph nodes	M ₀	Absent
Stage III _C	T _{4a}	Penetration to surface of visceral peritoneum	N _{2a}	Four to six lymph nodes	M ₀	Absent
	T _{3-4a}	As described above	N _{2b}	Seven or more lymph nodes	M ₀	Absent
	T _{4b}	Direct invasion into, or adherence [§] to, other structures	N ₁₋₂	As described above	M ₀	Absent
Stage IV _A	T _{any}	As described above	N _{any}	As described above	M _{1a}	One site*
Stage IV _B	T _{any}	As described above	N _{any}	As described above	M _{1b}	Multiple sites*

* M_{1a} refers to metastasis confined to one site (e.g.: liver, lung, ovary, non-regional lymph node) whereas M_{1b} refers to metastasis in more than one site or within the peritoneum.

§ 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).² 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
Stage 0	<ul style="list-style-type: none"> • 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. • No adjuvant systemic therapy is indicated.
Stage I	<ul style="list-style-type: none"> • Perform surgical resection with oncologic principles.^{3,4} • No adjuvant systemic therapy is indicated.
Stage II	<ul style="list-style-type: none"> • Perform surgical resection with oncologic principles. • No adjuvant chemotherapy is indicated unless at least one "high-risk feature" is present.⁵⁻⁸ • 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.⁹⁻¹² • "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, age under forty years, or evaluation of less than twelve regional lymph nodes.

Stage	Recommendations						
	<ul style="list-style-type: none"> 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.^{1,13,14} 						
Stage III	<ul style="list-style-type: none"> Perform surgical resection with oncologic principles. When compared to no adjuvant chemotherapy therapy, 5-Fluorouracil-based regimens reduce the relative risk of death by 30 to 36%.¹⁵⁻¹⁷ Adjuvant chemotherapy options include: <table border="1" data-bbox="277 541 1479 1287"> <tr> <td data-bbox="277 541 521 789">CAPOX/XELOX¹⁸</td> <td data-bbox="521 541 1479 789">Eight three-week cycles where Oxaliplatin 130 mg/m² is administered IV Q21d and Capecitabine 1,000 mg/m² is administered PO Q12h for fourteen days. Refer to "Capecitabine: A Guide for Patient Care." NO16968 demonstrated an improvement in both the disease-free survival (66.1% versus 59.8%, HR 0.80, CI_{95%} 0.69-0.93, <i>p</i> = 0.0045) and relapse-free survival (67.8% versus 60.9%, HR 0.78, CI_{95%} 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% versus 74.2%, HR 0.87, CI_{95%} 0.72-1.05, <i>p</i> = 0.1486), the Kaplan-Meier curves continue to separate.</td> </tr> <tr> <td data-bbox="277 789 521 1171">Modified FOLFOX^{9,19}</td> <td data-bbox="521 789 1479 1171">Twelve two-week cycles where <ul style="list-style-type: none"> Oxaliplatin (85 mg/m² IV over two hours) and Leucovorin (400 mg/m² IV over two to six hours) are administered concurrently, Followed by 5-Fluorouracil (400 mg/m² IV bolus), Followed by a continuous intravenous infusion of 5-Fluorouracil (2,400 mg/m² over forty-six hours). 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% versus 58.9%, HR 0.78, CI_{95%} 0.65-0.93, <i>p</i> = 0.005) and six-year overall survival (72.9% versus 68.7%, HR 0.80, CI_{95%} 0.65-0.97, <i>p</i> = 0.023). The benefit of Oxaliplatin in patients over seventy years of age has been questioned.^{10-12,20}</td> </tr> <tr> <td data-bbox="277 1171 521 1287">Capecitabine²¹</td> <td data-bbox="521 1171 1479 1287">Eight three-week cycles where Capecitabine 1,250 mg/m² is administered PO Q12h for fourteen days. Refer to "Capecitabine: A Guide for Patient Care." 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 1.12²⁴. However, given the cumulative-dose dependent toxicity of oxaliplatin²⁵, 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"> 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). 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). <p>Other regimens may be considered in specific clinical situations:</p> <ol style="list-style-type: none"> Mayo Regimen:^{22,23} Six four-week cycles where Leucovorin 20 mg/m² IV followed by 5-Fluorouracil 425 mg/m² IV are administered daily for five consecutive days. Roswell Park Regimen: Four eight-week cycles where Leucovorin (500 mg/m² IV over two hours) followed by 5-Fluorouracil (500 mg/m² IV bolus) are administered once every week for six weeks. 	CAPOX/XELOX ¹⁸	Eight three-week cycles where Oxaliplatin 130 mg/m ² is administered IV Q21d and Capecitabine 1,000 mg/m ² is administered PO Q12h for fourteen days. Refer to "Capecitabine: A Guide for Patient Care." 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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](#)).

GLOSSARY OF ABBREVIATIONS

Acronym	Description
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

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

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APPENDIX A

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

