

Metastatic Colorectal Cancer

Effective Date: February, 2021



Background

Generally, metastatic colorectal cancer represents an incurable situation for which only palliative options (e.g.: best supportive care, palliative chemotherapy) should be considered. However, there are specific circumstances where an attempt at metastatectomy (surgical resection of a metastasis) may be possible and where five-year survivals may reach 40 percent¹⁻³. In addition, cytoreductive surgery (“peritoneal stripping”) and heated intra-peritoneal chemotherapy may be considered for limited intra-peritoneal metastases⁴. Such treatments require involvement of a multidisciplinary team that should include a hepatobiliary surgeon, thoracic surgeon, and surgical oncologist (see Appendix A [\[Link\]](#)). Consider post-operative (“adjuvant”) therapy (an extrapolation from Clinical Practice Guidelines for [Early Stage Colon Cancer](#)) along with careful surveillance for patients with no evidence of residual disease (also an extrapolation from Clinical Practice Guidelines for [Colorectal Cancer Surveillance](#)):

Post-Metastatectomy Colorectal Cancer Surveillance Guidelines⁵

If resection of another recurrence from liver and/or lung is clinically appropriate,

- Obtain a CEA every three months for five years (progressive rises warrant a workup for recurrent disease); and
- Obtain a CT scan of the thorax, abdomen, and pelvis at the discretion of the treating physician.

Radiofrequency ablation⁶ (RFA) or other local therapies may be considered for patients with otherwise resectable liver metastases who are unable to consider surgery due to medical comorbidities (e.g.: lung disease, significant heart disease).

It is recommended that surgery (e.g.: colon resection, diverting colostomy), endoscopic procedure (e.g. stent placement), or radiotherapy be considered to relieve or prevent a bowel obstruction. This may not be required in a patient with an asymptomatic (or minimally symptomatic) primary colorectal cancer and clearly incurable metastatic disease.

Palliative chemotherapy regimens are generally continued as long as tumor shrinkage or stability is confirmed, the side effects remain manageable, the patient wishes to continue, and the treatment remains medically reasonable. Palliative radiotherapy may help control local problems (e.g. pain from bone metastases, bleeding from *in situ* rectal cancer).

Guideline Questions

1. What are the recommended treatment regimens for adult patients with metastatic colorectal cancer?

Search Strategy

This guideline was developed to outline the management recommendations for patients with metastatic colorectal cancer. 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. The most recent update involved the following search criteria using the Pubmed database: (("secondary"[Subheading] OR "secondary"[All Fields] OR "metastatic"[All Fields]) AND ("colorectal neoplasms"[MeSH Terms] OR ("colorectal"[All Fields] AND "neoplasms"[All Fields]) OR "colorectal neoplasms"[All Fields] OR ("colorectal"[All Fields] AND "cancer"[All Fields]) OR "colorectal cancer"[All Fields])) AND (Clinical Trial, Phase III[ptyp] AND ("2019/01/01"[PDAT] : "2020/12/12"[PDAT])).

Target Population

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

Recommendations

Goals of Therapy

1. To maintain or to improve the patient's quality of life (to control or to delay the onset of tumour-related symptoms).
2. To prolong life, if possible.

Recommendations

1. Consider treatment on a clinical trial, if available.
2. Patients with a new diagnosis of metastatic disease (stage IV diagnosis) should receive testing for activating mutations of Ras (Kras and Nras), BRAF, and evaluation of microsatellite instability or mismatch repair deficiency in tumour tissue.
3. In the absence of relevant comorbid medical problems, patients with metastatic colorectal cancer and a performance status of ECOG 0, 1, or 2 should be offered palliative chemotherapy.

Table 1. ECOG Performance Status Scale.

ECOG	Description
0	Fully active and able to carry on without restriction.
1	Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care and/or confined to a bed or chair for more than 50% of waking hours.

4 Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.

4. Patients with metastatic colorectal cancer who will receive cancer therapy should receive a baseline CT chest, abdomen, and pelvis. Additional baseline imaging is appropriate if symptoms are suggestive of metastases (e.g. CT head, bone scan). Further imaging for potential surgical candidates may necessitate an MRI for liver metastases or rectal primaries, and PET CT for other regions. While on systemic therapy, imaging should be done every 2-3 months depending on the clinical scenario.

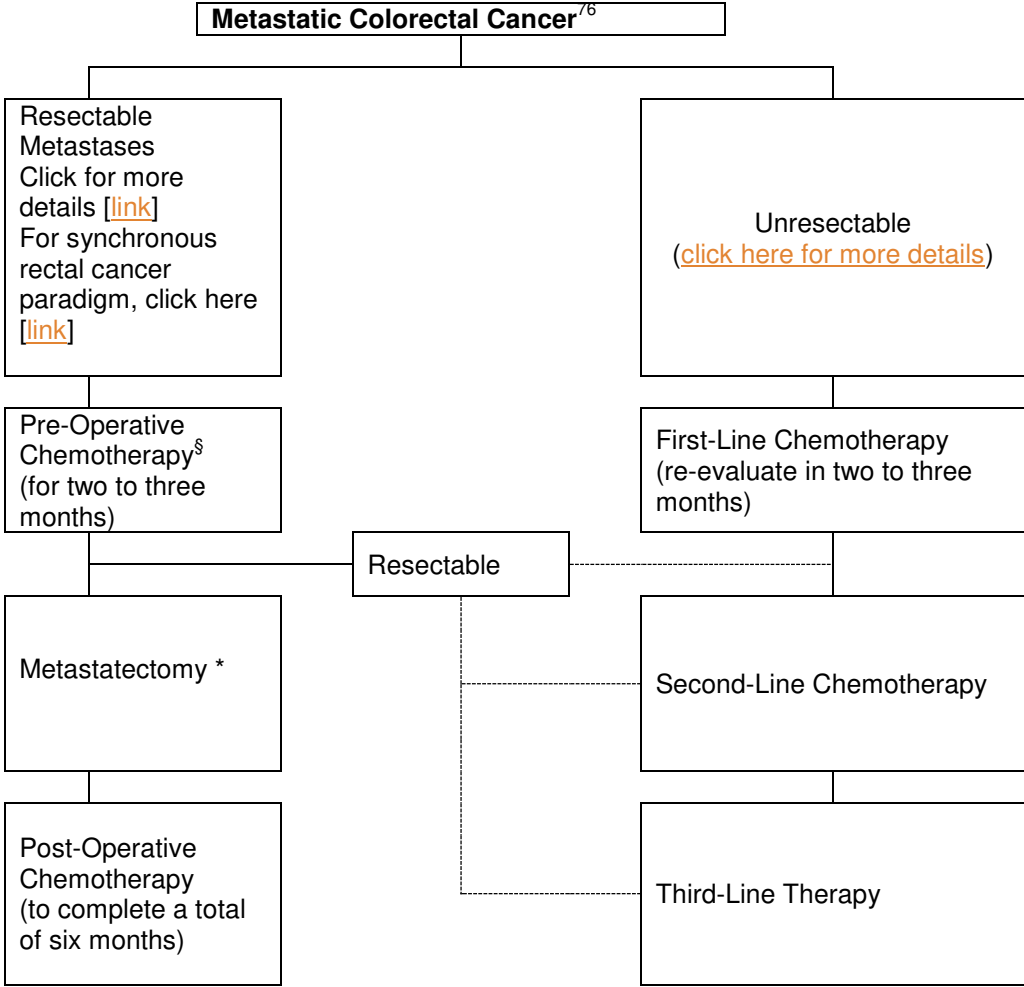
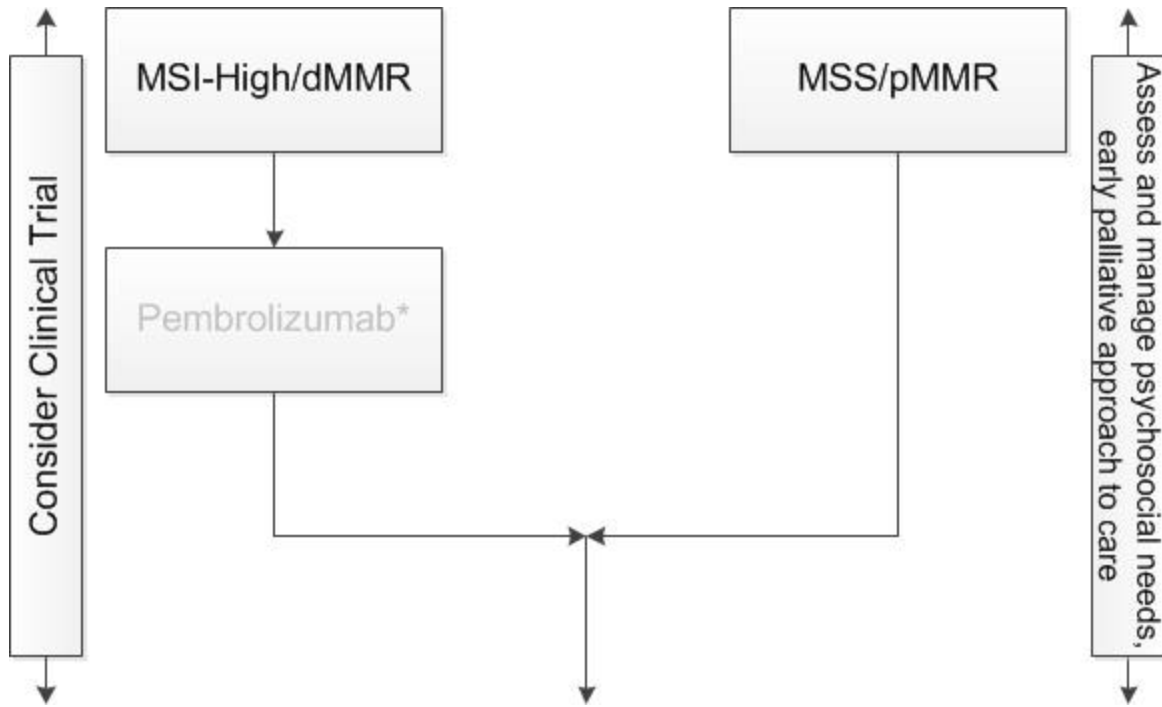


Figure 1. Algorithm for Metastatic Colorectal Cancer Treatment

[^] Encourage the discussion of patients at multidisciplinary rounds.

^{*} Resection may require multiple procedures. Liver resection may require a portal vein embolization
SBRT (SBRT=Stereotactic Body Radiotherapy) can be considered when alternative therapies have failed or are contraindicated, or for palliation of symptoms.



BRAF Mutant	RAS Wild Type - Left Sided Primary	RAS Wild Type - Right Sided Primary	RAS Mutant
Consider FOLFOXIRI Bevacizumab ¹	FOLFOX/CAPOX or FOLFIRI ± EGFR ¹	FOLFOX/CAPOX or FOLFIRI ± Bevacizumab ¹	
Encorafenib + Cetuximab*	Alternative doublet ± Bevacizumab ¹	Alternative doublet ± Bevacizumab (if not used in the first line) ¹	
	Panitumumab if not used in the first line		
Trifluridine tipiracil* or Regorafenib* or Clinical Trial			

Subsequent lines of therapy

Or Alternative Chemotherapy Options Include:

Capecitabine/5FULV/Ralitrexed
Irinotecan
FOLFOX or CAPOX ± Bevacizumab ¹
Panitumumab if RAS wild type
Trifluridine tipiracil* or Regorafenib* or Clinical Trial

Subsequent lines of therapy

¹If clinically appropriate

*Not available on provincial formulary

Figure 2. Chemotherapy options for Unresectable Metastatic Colorectal Cancer Consider an Early Palliative Approach to Care, More information: [\[Link\]](#)

5. The location of the tumour within the colon (proximal/distal) appears to be important. A multivariate analysis of 1,437,846 patients in sixty-six trials published between 1995 and 2016 demonstrated that the location of the primary tumor site in the distal (left-sided) (*versus* proximal or right-sided) colon is associated with a better survival (HR 0.82, CI_{95%} 0.79-0.84, $p < 0.001$)⁷. Beyond outcome, differences in epidemiology, pathogenesis, genetic and epigenetic alterations, and molecular pathways are now recognized between proximal and distal primary tumor sites⁸:

Pooled retrospective analyses establish the predictive and prognostic value of primary tumor site using Cetuximab and Panitumumab^{9,10}. In a retrospective evaluation of 38% of the 5,760 patients enrolled in the *CRYSTAL*, *FIRE-3*, *PEAK*, *PRIME*, *181*, and *CALGB 80405* studies (trials with different populations, control arms, treatments, etc.), primary tumor location confers both prognostic effect (outcomes are worse for disease that arises from the proximal colon, regardless of the treatment received) and predictive effect (first-line use of anti-EGFR therapy improves outcomes in *RAS* wild-type disease that arises from the distal colon but offers no benefit when disease arises from the proximal colon)¹¹. Selection of first-line therapy should now consider the results of a rigorous molecular analysis as well as reference to the primary tumor location (in addition to patient preferences, extent of cancer, goals of care, mutations in *RAS*, medical comorbidities, performance status, etc.).

6. Standard palliative chemotherapy regimens to consider are described in Table 2 [\[link\]](#).
7. (*Kras* and *Nras*) predict a lack of response in anti-Epidermal Growth Factor Receptor (EGFR) therapy in patients with metastatic colorectal cancer²⁸. Patients with known *Ras* mutations should not be treated with either cetuximab or panitumumab.
 - a. Note: The recommendation for *Ras* testing should not necessarily indicate a preference regarding regimen selection in the first-line setting. Rather, early identification of *Ras* status is intended to plan for the treatment continuum.
 - b. When compared to best supportive care in patients with *Kras* wild-type colorectal cancer refractory or intolerant to a fluoropyrimidine (e.g.: 5-Fluorouracil, Capecitabine), Irinotecan, and Oxaliplatin, the use of monoclonal antibodies directed at the EGFR delays disease progression and deterioration in quality of life. Panitumumab administered at 6 mg/kg IV over sixty minutes every two weeks prolongs progression-free survival^{34,35}. Only Panitumumab is funded for patients with *Kras* wild-type disease on the Alberta Health Services Cancer Drug Benefit Program. Refer to the [Panitumumab and Cetuximab: Toxicity Management Guidelines](#).

The EGFR signaling pathway is activated in response to binding of the ligand to the extracellular domain of the EGFR. The resultant signaling cascade regulates genes that control progression through the cell cycle. *Kras* regulates this cascade. The *Kras* gene may be “wild-type” (in up to 65% of cases) or “mutated”. Wild-type *Kras* remains active only transiently after interaction of EGFR with its ligand. Mutated *Kras* remains constitutively active irrespective of activation of EGFR. This permits unregulated proliferation and enhances survival, metastasis, and angiogenesis.

Monoclonal antibodies directed against EGFR block activation of the EGFR and, thereby, the downstream events. A constitutively active (“mutant”) *Kras* would not be influenced by such therapy.

Kras testing by quantitative PCR (or direct DNA sequencing) is highly specific for mutations known to confer constitutive activation.

8. The Alberta Provincial Gastrointestinal Tumour Team supports the use of EGFR inhibitors in first-line treatment for patients with *Ras* wild-type metastatic colorectal cancer (i.e. non-mutated *Kras* or *Nras*) with left sided primary tumors.
9. Patients with BRAF mutated metastatic colorectal cancer represent a distinct group of patients who have a poor prognosis and are typically resistant to traditional doublet chemotherapy regimens. The individual patient data meta-analysis of 5 trials compared FOLFOXIRI + bevacizumab versus doublet chemotherapy + bevacizumab, including n=115 patients with BRAF mutations. FOLFOXIRI + bevacizumab had increased response rates for patients with BRAF mutations. This regimen is associated with increased neutropenia, febrile neutropenia, and diarrhea. There was no significant improvement in OS or PFS with FOLFOXIRI + bevacizumab compared to doublet chemotherapy + bevacizumab⁷⁹. In select patients with BRAF mutations, FOLFOXIRI + bevacizumab may be considered.
For patients who have progressed on first or second line treatments (i.e. those that have been exposed to both irinotecan and oxaliplatin), the combination of BRAF, MEK and EGFR inhibition appears to be effective. The phase III open-label BEACON trial studied 665 patients with BRAF V600E mutated metastatic colorectal cancer. Patients had progressed on 1 or 2 prior treatments³⁷. They were randomized to encorafenib, binimetinib and cetuximab, encorafenib and cetuximab or dealer's choice of irinotecan+ cetuximab or FOLFIRI plus cetuximab (argued to be the standard treatment). The analysis was powered to compare the triplet regimen against the standard treatment arm. In an updated overall survival analysis, median OS was similar in patients treated with encorafenib + cetuximab with or without binimetinib (9.3 mo and 9.3 mo, respectively). Median OS in the standard treatment arm was 5.9 mo. Treatment with encorafenib + cetuximab with or without binimetinib was associated with longer maintenance of quality of life across different QOL assessment tools compared to the standard arm⁸⁰. Encorafenib and cetuximab is not currently funded in Alberta. In the absence of access to cetuximab, and the specific BRAF and MEK inhibitors used in this trial, a similar option is a combination of panitumumab, dabrafenib and trametinib, which has proven to be a safe regimen³⁸.
10. Whether treatment is with combination chemotherapy or sequential monotherapy (with or without Bevacizumab) depends upon the patient's goals, their physical status, and other life circumstances, as assessed by their treating oncologist. Sequences of therapy may include:
 - a. FOLFIRI followed by CAPOX/FOLFOX6
 - b. CAPOX/FOLFOX6 followed by FOLFIRI or Irinotecan
 - c. Capecitabine followed by Irinotecan followed by CAPOX/FOLFOX6
11. For patients with MSI-high or dMMR metastatic colorectal cancer (approximately 3.5% of cases⁸¹), pembrolizumab improves progression-free survival compared to standard chemotherapy (median 16.5 months vs. 8.2 mo, HR: 0.60; 95%CI: 0.45-0.80, p=0.0002), with a lower incidence of grade 3 or higher adverse events (22% vs. 66%) and delays time to

deterioration in quality of life⁸². Pembrolizumab is not currently funded in Alberta. Patients with a deletion in MLH1 and a BRAF mutation likely have a sporadic mutation and do not necessarily need a referral to genetics. A referral to genetics should be offered for all other patients that are MSI-high or dMMR.

12. Patients who present with resectable lung or liver metastasis should be discussed in multidisciplinary rounds. Patients that may proceed directly to metastatectomy for liver metastasis can be considered for perioperative FOLFOX4 chemotherapy delivered 3 months pre-hepatic resection and 3 months post-hepatic resection. The EORTC Intergroup trial 40983 demonstrated an improvement in PFS, but not necessarily overall survival. The 5-year OS in this trial was approximately 50%⁸³. The addition of cetuximab to FOLFOX in this setting is not appropriate.
13. In the situation where a liver metastatectomy would be facilitated by a reduction in the size of the liver metastasis, patients should only be treated with chemotherapy until optimal resectability rather than to maximal response or progression. Only a limited number of cycles of chemotherapy should be delivered so as to minimize the consequences to the liver and their adverse effects. Oxaliplatin-based therapy is less likely to impact on post-metastatectomy mortality than Irinotecan-based therapy³⁹. For patients who are not upfront resectable the addition of biological agents is controversial. The general approach for consideration of a biologic agent for non-liver limited mCRC should be used. Kras wild type, left sided primary, consider panitumumab⁸⁵; Kras mutant, consider bevacizumab.⁸⁶ For patients who have resection of liver metastases with no residual disease, give subsequent consideration to "adjuvant" chemotherapy to complete a total course of therapy equivalent to six months (see Early Stage Colon Cancer Guideline [here](#)). See Appendix A: "Approach to Metastatic Colorectal Cancer" [[link](#)].

Table 2. Palliative Chemotherapy Regimens for Patients with Metastatic Colorectal Cancer.

Regimen	Details
FOLFIRI ¹²	<ul style="list-style-type: none"> • Involves the administration of Irinotecan (180 mg/m² IV) and Leucovorin (400 mg/m² IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m² IV bolus and then an IV infusion of 2,400 mg/m² over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • For patients who have complications with, or contraindications to, placement of a port, CVC, or PICC along with the capacity to tolerate the potential for greater toxicity, consider CAPIRI (administers Irinotecan 200 mg/m² IV over ninety minutes followed by Capecitabine 800 mg/m² PO Q12h for fourteen days in every twenty-one day cycle).⁷⁸ • Supplement with Bevacizumab, where appropriate (see below). • Consider a switch to FOLFOX6 (or CAPOX) at progression, provided it is medically reasonable and the patient wishes further therapy. The sequence of FOLFIRI followed by FOLFOX6 is equivalent to the sequence of FOLFOX6 followed by FOLFIRI¹². • Due to Oxaliplatin's propensity to cause a cumulative peripheral sensory neuropathy, consider a non-Oxaliplatin-containing regimen before an Oxaliplatin-

Regimen	Details
	<p>based regimen.</p> <p>Irinotecan should be considered relatively contraindicated (or consider a dose modification) for patients with an elevated bilirubin due to metastatic disease or Gilbert's syndrome</p> <ul style="list-style-type: none"> • Gilbert's syndrome results from impaired activity of uridine diphosphate glucuronyl-transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of <u>Irinotecan</u> and thereby increases the risk of severe toxicity.
CAPOX and mFOLFOX6 ¹²⁻¹⁴	<ul style="list-style-type: none"> • CAPOX involves the administration of Oxaliplatin (130 mg/m² IV over two hours) and Capecitabine 1,000 mg/m² PO Q12h for fourteen days in every twenty-one day cycle. • mFOLFOX6 involves the administration of Oxaliplatin (85 mg/m² IV) and Leucovorin (400 mg/m² IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m² IV bolus and then an intravenous infusion of 2,400 mg/m² over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • Supplement with Bevacizumab, where appropriate (see below). • Consider a switch to FOLFIRI or Irinotecan at progression, provided it is medically reasonable and the patient wishes further therapy. The sequence of FOLFIRI followed by FOLFOX6 is equivalent to the sequence of FOLFOX6 followed by FOLFIRI¹². • Due to Oxaliplatin's propensity to cause a cumulative peripheral sensory neuropathy, consider a non-Oxaliplatin-containing regimen before an Oxaliplatin-based regimen. • For patients with persistent grade ≥ 2 peripheral neuropathy, considering holding or reducing the doses of Oxaliplatin.
FOLFOXIRI ¹⁵	<ul style="list-style-type: none"> • Involves the administration of a 90 minute infusion of Irinotecan (165 mg/m²), a 120 minute infusion of Oxaliplatin (85 mg/m²), and a concomitant 120 minute infusion of Leucovorin (400 mg/m²), followed by a 48-hour continuous infusion 5-Fluorouracil (total dose 3200 mg/m²) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). • Supplement with Bevacizumab, where appropriate (see below). • FOLFOXIRI is usually reserved for patients with excellent performance status as the progression free survival and overall survival improvement associated with FOLFOXIRI and Bevacizumab in the TRIBE study were accompanied with increased toxicity¹⁵.
Capecitabine ¹⁶	<ul style="list-style-type: none"> • Involves the administration of Capecitabine 1,250 mg/m² PO Q12h for fourteen days in every twenty-one day cycle. Refer to "Capecitabine: A Guide for Patient Care." • Supplement with Bevacizumab, where appropriate (see below).
Irinotecan ¹⁷	<ul style="list-style-type: none"> • Involves the administration of Irinotecan (350 mg/m² IV over ninety minutes) in every three-week cycle. • Decrease the dose by 20% for patients over seventy years of age or for patients who have received prior radiotherapy to the pelvis. <p>Irinotecan should be considered relatively contraindicated (or consider a dose modification) for patients with an elevated bilirubin due to metastatic disease or Gilbert's syndrome</p> <ul style="list-style-type: none"> • Gilbert's syndrome results from impaired activity of uridine diphosphate glucuronyl-transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of <u>Irinotecan</u> and thereby increases the risk of severe toxicity.

Regimen	Details																																		
5-Fluorouracil (simplified LV5FU2)	<ul style="list-style-type: none"> Involves the administration of Leucovorin (400 mg/m² IV over two hours) followed by 5-Fluorouracil (400 mg/m² IV bolus and then an intravenous infusion of 2,400 mg/m² over forty-six hours) in every two-week cycle. This regimen requires placement of a port, central venous catheter (CVC), or peripherally inserted central catheter (PICC). Supplement with Bevacizumab, where appropriate (see below). 																																		
Raltitrexed ¹⁸	<ul style="list-style-type: none"> Considered for patients intolerant of 5-Fluorouracil Involves the administration of Raltitrexed IV at a dose and frequency that is based on the patient's creatinine clearance. <table border="1"> <thead> <tr> <th>Creatinine Clearance</th> <th>Dose as Percentage of 3 mg/m²</th> <th>Interval</th> </tr> </thead> <tbody> <tr> <td>> 65 mL/minute</td> <td>100%</td> <td>Q3weeks</td> </tr> <tr> <td>55 to 65 mL/minute</td> <td>75%</td> <td>Q4weeks</td> </tr> <tr> <td>25 to 54 mL/minute</td> <td>% Equivalent to Creatinine Clearance</td> <td>Q4weeks</td> </tr> <tr> <td>< 25 mL/minute</td> <td>No therapy</td> <td>Not applicable</td> </tr> </tbody> </table>	Creatinine Clearance	Dose as Percentage of 3 mg/m ²	Interval	> 65 mL/minute	100%	Q3weeks	55 to 65 mL/minute	75%	Q4weeks	25 to 54 mL/minute	% Equivalent to Creatinine Clearance	Q4weeks	< 25 mL/minute	No therapy	Not applicable																			
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Bevacizumab ^{16, 19-23}	<ul style="list-style-type: none"> Bevacizumab interrupts VEGF-mediated angiogenesis — a critical factor in tumor growth and progression. It is thought to decrease the interstitial pressure in tumors, to normalize tumor vasculature, and to improve the delivery of chemotherapy. Bevacizumab is contraindicated in patients with: <ul style="list-style-type: none"> Radiological or clinical evidence of invasion of the tumor into a major blood vessel; Major surgical procedure or significant trauma within preceding twenty-eight days; Major surgical procedure anticipated within forthcoming four to six weeks; Uncontrolled hypertension; Clinically significant cardio- or cerebro-vascular disease (e.g.: myocardial infarction or cerebrovascular accident within six months, unstable angina, congestive heart failure, use of a thrombolytic agent within six months, serious dysrhythmia); Inherited bleeding diathesis, coagulopathy, or esophageal varices; Significant proteinuria or renal dysfunction; Non-healing wound, ulcer, or bone fracture; Metastases within central nervous system or ophthalmologic abnormalities; and Pregnancy, lactation, or childbearing potential without effective contraception. If the medical oncologist feels the benefits outweigh the risks, it may be combined with chemotherapy in patients with a good performance status (ECOG ≤2). It can be administered over ten minutes at 5 mg/kg IV (Q2week chemotherapy schedule) or over fifteen minutes at 7.5 mg/kg IV (Q3week chemotherapy schedule). <table border="1"> <thead> <tr> <th rowspan="2">Toxicities</th> <th colspan="2">Summary Incidence</th> <th colspan="2">Relative Risk</th> </tr> <tr> <th>All-Grade Events</th> <th>High-Grade Events</th> <th>All-Grade Events</th> <th>High-Grade Events</th> </tr> </thead> <tbody> <tr> <td>Arterial Thromboembolic Events¹⁹</td> <td>3.3%</td> <td>2.0%</td> <td>HR 2.08</td> <td>HR 1.29</td> </tr> <tr> <td> Cardiac Ischemia</td> <td></td> <td>1.5%</td> <td></td> <td>HR 2.14</td> </tr> <tr> <td> Cerebrovascular Ischemia</td> <td></td> <td>1.2%</td> <td></td> <td>HR 1.37</td> </tr> <tr> <td>Proteinuria²²</td> <td>—</td> <td>1.0%</td> <td>HR 1.40</td> <td>—</td> </tr> <tr> <td>Hypertension²²</td> <td>—</td> <td>8.7%</td> <td>—</td> <td>HR 3.00</td> </tr> </tbody> </table>	Toxicities	Summary Incidence		Relative Risk		All-Grade Events	High-Grade Events	All-Grade Events	High-Grade Events	Arterial Thromboembolic Events ¹⁹	3.3%	2.0%	HR 2.08	HR 1.29	Cardiac Ischemia		1.5%		HR 2.14	Cerebrovascular Ischemia		1.2%		HR 1.37	Proteinuria ²²	—	1.0%	HR 1.40	—	Hypertension ²²	—	8.7%	—	HR 3.00
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	Wound Healing Complications ^{20,21,24}	4.9%	3.7%	—	—
	Gastrointestinal Perforation ²⁵	—	0.9%	—	HR 2.15
	<ul style="list-style-type: none"> Discrepant results exist as to the risk of venous thromboembolic events^{23,26} It is not indicated for monotherapy and it is currently not funded by the Alberta Health Services Cancer Drug Benefit Program for treatment beyond progression. <ul style="list-style-type: none"> Refer to the Bevacizumab Administration Guidelines. 				
EGFR inhibitor and chemotherapy ²⁷⁻²⁹	<ul style="list-style-type: none"> First-line anti-EGFR therapies may include: <ol style="list-style-type: none"> Cetuximab with FOLFIRI²⁷ Panitumumab with FOLFOX²⁸ Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)²⁹ EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome^{30,31}. Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines 				

14. Patients who have progressed on all standard therapy should be encouraged to participate in clinical trials.

The following trials have been conducted in patients who have progressed on or were intolerant to a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR inhibitor (if KRAS/NRAS wild type):

The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib. OS for patients on regorafenib was 6.4 months versus 5.0 months for the placebo arm (HR 0.77, 95% CI 0.64–0.94, p=0.005). PFS improved modestly but significantly (1.9 months versus 1.7 months; HR 0.49, 95% CI 0.42 – 0.58, p<0.000001). The most common adverse events observed in the trial were hand-foot skin reactions (17%), fatigue (10%), hypertension (7%), diarrhea (7%) and rash/desquamation (6%). Regorafenib is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program.

The phase III RECOURSE trial randomized 800 patients to trifluridine-tipiracil or placebo. Median OS was significantly prolonged in patients treated with trifluridine-tipiracil compared to placebo (7.1 versus 5.3 months, HR 0.68, 95% CI 0.58- 0.81; P<0.001), and this benefit was irrespective of prior regorafenib use. Trifluridine-tipiracil is currently not funded by the Alberta Health Services Outpatient Cancer Drug Benefit Program⁴⁰.

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Appendix A: Approach to Metastatic Colorectal Cancer

Resectable lung or liver metastases	<ul style="list-style-type: none"> • Proceed directly to metastatectomy and give subsequent consideration to six months of “adjuvant” chemotherapy. • Perioperative FOLFOX4, with 3 months pre-hepatic resection and 3 months post-hepatic resection can be considered for patients with resectable liver metastases. The EORTC Intergroup trial 40983 demonstrated an improvement in progression free survival^{41,42}, but not necessarily overall survival. The 5-year overall survival in this trial was approximately 50% • For patients with metastatic colorectal cancer, optimal palliative chemotherapy offers two-year survivals under 40% and five-year survivals under 5% whereas resection of liver metastases offers two-year survivals of 60% to 70% and five-year survivals of 30%. • Resection of lung metastases offers a five-year overall survival of 48% (39.6% for R₀ and 0% for R₁ or R₂ resections)³. • Assigning one point to each factor (node-positive primary, disease-free interval under twelve months, two or more hepatic metastases, largest metastasis over 5 cm, and CEA level over 200 µg/L) to generate a clinical risk (“Fong”) score; it is highly predictive of outcome². 																																																												
	<table border="1"> <thead> <tr> <th rowspan="2">“Fong Score”</th> <th colspan="6">Survival</th> </tr> <tr> <th>One-Year</th> <th>Two-Year</th> <th>Three-Year</th> <th>Four-Year</th> <th>Five-Year</th> <th>Median</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>93%</td> <td>79%</td> <td>72%</td> <td>60%</td> <td>60%</td> <td>6.2 Years</td> </tr> <tr> <td>1</td> <td>91%</td> <td>76%</td> <td>66%</td> <td>54%</td> <td>44%</td> <td>4.3 Years</td> </tr> <tr> <td>2</td> <td>89%</td> <td>73%</td> <td>60%</td> <td>51%</td> <td>40%</td> <td>3.9 Years</td> </tr> <tr> <td>3</td> <td>86%</td> <td>67%</td> <td>42%</td> <td>25%</td> <td>20%</td> <td>2.8 Years</td> </tr> <tr> <td>4</td> <td>70%</td> <td>45%</td> <td>38%</td> <td>29%</td> <td>25%</td> <td>1.7 Years</td> </tr> <tr> <td>5</td> <td>71%</td> <td>45%</td> <td>27%</td> <td>14%</td> <td>14%</td> <td>1.8 Years</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • The definition of resectable liver metastases continues to evolve. Currently, resection is considered possible if both an R₀ resection and an adequate* future liver remnant are anticipated, and two contiguous liver segments can be preserved. • For patients with a normal liver, hepatic insufficiency is rare when the future liver remnant exceeds 20% of the total liver volume⁴⁰. For patients extensively pre-treated with chemotherapy, a future liver remnant that exceeds 30% of the total liver volume is required. For patients with underlying liver disease (e.g.: cirrhosis), a future liver remnant that exceeds 40% of the total liver volume is necessary to avoid cholestasis, fluid retention, and liver failure. • The use of EGFR inhibitors for resectable colorectal liver metastases is not recommended. The New EPOC trial randomized operable metastatic patients with KRAS wild-type metastatic colorectal cancer to FOLFOX with or without cetuximab. The addition of cetuximab was associated with significantly worse PFS (median 15.5 mo vs. 22.2 mo) and OS (median 81.0 mo vs. 55.4 mo; HR: 1.45; 95%CI: 1.02-2.05; p=0.036)⁸⁴. 							“Fong Score”	Survival						One-Year	Two-Year	Three-Year	Four-Year	Five-Year	Median	0	93%	79%	72%	60%	60%	6.2 Years	1	91%	76%	66%	54%	44%	4.3 Years	2	89%	73%	60%	51%	40%	3.9 Years	3	86%	67%	42%	25%	20%	2.8 Years	4	70%	45%	38%	29%	25%	1.7 Years	5	71%	45%	27%	14%	14%
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5	71%	45%	27%	14%	14%	1.8 Years																																																							

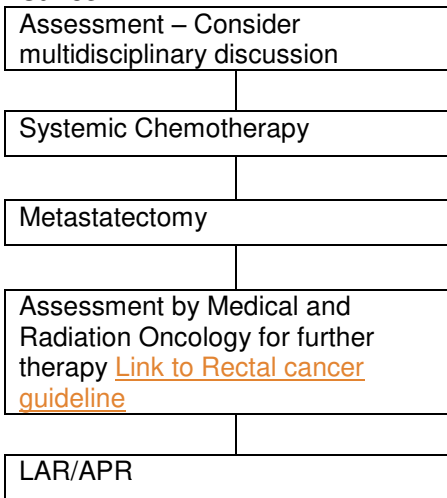
<p>Marginally resectable liver metastases</p>	<ul style="list-style-type: none"> • Pre-operative chemotherapy can downsize tumors^{43,44}, identify responders (progression predicts for a poor outcome)⁴⁴, and improve three-year progression-free survival (42.4% <i>versus</i> 33.2% in resected patients, HR 0.73, CI_{95%} 0.55-0.97, <i>p</i> = 0.025)⁴¹. • In the situation where a liver metastatectomy could be facilitated by reduction in the size of the liver metastasis, patients should be treated with Oxaliplatin-based chemotherapy to optimal resectability rather than to maximal response or progression. <p>The general approach for consideration of a biologic agent for non-liver limited mCRC should be used. Kras wild type, left sided primary, consider panitumumab⁸⁵; Kras mutant, consider bevacizumab.⁸⁶</p> <ul style="list-style-type: none"> • As the post-operative morbidity increases with the number of cycles of chemotherapy administered pre-operatively, only a limited number of cycles of chemotherapy should be delivered⁴⁵. The type of hepatic injury is regimen specific⁴⁶: <ul style="list-style-type: none"> • 5-Fluorouracil predisposes to steatosis, a typically indolent manifestation of non-alcoholic fatty liver disease (NAFLD) that can increase the risks of post-operative infectious complications. • Irinotecan predisposes to non-alcoholic steatohepatitis (NASH), a serious complication of non-alcoholic fatty liver disease that includes fatty infiltration, inflammation, and hepatocyte damage. This can affect the hepatic reserve and increase morbidity and mortality after partial hepatectomy (ninety-day mortality of 1.6% <i>versus</i> 14.7%, <i>p</i> = 0.001)³⁹. • Oxaliplatin predisposes to sinusoidal obstruction (characterized by peri-sinusoidal inflammation, congestion, fibrosis, and venous occlusion). Some studies³⁹ suggest that it fails to increase the risk of peri-operative death while others⁴⁷ suggest that it increases morbidity (from 6.3% to 40.0%, <i>p</i> < 0.026) and prolongs length-of-stay (from 10.9 days to 17.0 days, <i>p</i> < 0.006) after hepatectomy. • Bevacizumab reduces the sinusoidal dilation induced by Oxaliplatin (all grades: from 53.5% to 27.4%; moderate or severe grades: from 27.9% to 8.1%, <i>p</i> < 0.01) as well as the degree of tumor viability when used in combination with 5-Fluorouracil and Leucovorin (32.9% <i>versus</i> 45.3%, <i>p</i> = 0.02)⁴⁸. Bevacizumab fails to impair liver regeneration after portal vein embolization⁴⁹. • In a retrospective analysis of patients with initially unresectable metastatic disease⁵⁰, 12.5% became resectable after pre-operative FOLFOX. This was associated with a five-year survival of 33% — similar to the results achieved in “initially operable” patients. • In a retrospective analysis of patients who underwent pre-operative chemotherapy and resection of colorectal liver metastases, the degree of pathologic response correlated with outcome (five-year survival of 75% for complete response, 56% for major response, and 33% for minor response). The predictors for complete or major response were CEA ≤ 5 µg/L, tumor size ≤ 3 cm, and chemotherapy with fluoropyrimidine, Oxaliplatin, and Bevacizumab⁵¹. • Portal vein occlusion by pre-operative embolization or intra-operative ligation can increase the volume of the left lobe by 30 to 40%. Metastases in the future liver remnant should be resected before portal vein embolization⁵². • The addition of Oxaliplatin^{53,54} but not Irinotecan⁵⁵⁻⁵⁷ to 5-Fluorouracil and Leucovorin in the adjuvant treatment of stage III colon cancer improves outcomes. Therefore, if the metastatic disease is resected, give subsequent consideration to “adjuvant” chemotherapy to complete a total course of therapy equivalent to six months (see Clinical Practice Guidelines for Early Stage Colon Cancer)⁵⁸.
<p>Radiofrequency ablation</p>	<ul style="list-style-type: none"> • Radiofrequency ablation applies multiple four- to six-minute cycles of current to create irreversible damage and protein coagulation around a percutaneously-placed needle. It can be applied to liver metastases under 5 cm (preferably under 3 cm) that are located away from large blood vessels (“heat sinks”). Although hemorrhage, bile leak, and infection can occur, major complications arise in only about 2% of patients treated. Incomplete ablation is identified in 20 to 30% of cases. While needle-track recurrences occur, this is reduced by ablation upon withdrawal. Retrospective studies⁵⁹⁻⁶¹ suggest that radiofrequency ablation is associated with a higher local recurrence rate and a lower recurrence-free and overall survival when compared to resection of a hepatic metastasis.
<p>Peritoneal carcinomatosis</p>	<ul style="list-style-type: none"> • Cytoreductive surgery in combination with heated intra-peritoneal chemotherapy (HIPEC) followed by systemic 5-Fluorouracil and Leucovorin provides superior outcomes when compared to the same systemic chemotherapy regimen with or without palliative surgery

	<p>(median survival 22.3 months <i>versus</i> 12.6 months, HR 0.55, CI_{95%} 0.32-0.95, $p = 0.032$)⁶². Patients with involvement of zero to five of the seven regions of the abdominal cavity have a significantly better survival than patients with six or seven affected regions. Macroscopically complete cytoreduction (R₁) confers a significantly superior survival than patients with residual disease (R₂).</p> <ul style="list-style-type: none"> • Cytoreductive surgery⁶³ involves the complete removal of macroscopic disease (e.g.: peritonectomy, omentectomy, cholecystectomy, splenectomy, abdominal organs involved with tumor), lysis of intra-abdominal adhesions (to permit optimal exposure to heated intra-peritoneal chemotherapy), and reconstitution of the gastrointestinal tract. Hyperthermia exerts a direct cytotoxic effect that impairs DNA repair, denatures proteins, induces heat-shock proteins, induces apoptosis, inhibits angiogenesis, and blocks oxidative metabolism⁶⁴. Hyperthermia is synergistic with cytotoxic agents⁶⁵. The process is associated with a reported morbidity and mortality rates of 22.9% and 4%, respectively⁶⁶.
Unresectable disease	<ul style="list-style-type: none"> • Consider palliative chemotherapy. click here for more details • Resection of an asymptomatic primary colorectal cancer provides only minimal palliative benefit, risks morbidity and mortality, and delays initiation of systemic therapy^{67,68}. Obstruction and bleeding complicate only 13.9% and 3.0% of cases treated with palliative chemotherapy when the primary tumor is left <i>in situ</i>. Therefore, when a patient presents with an unequivocally unresectable metastatic disease and an asymptomatic primary colorectal cancer, palliative chemotherapy can be initiated; resection of the primary tumor can be reserved for the small proportion of patients who develop a complication related to the primary tumor. Resection, diversion, placement of a stent, or radiation is indicated for a symptomatic primary colorectal cancer.
Stereotactic Body Radiotherapy (SBRT)	<ul style="list-style-type: none"> • Liver SBRT is used to deliver high doses of radiation accurately to ablate and destroy all normal and tumour cells within a small geographic area. SBRT can provide moderate rates of local control for patients with liver metastases (50-100% at 1 year, 45-80% at 2 years), however, literature is limited to single institution retrospective studies⁶⁹⁻⁷⁵. • Patients should be discussed at multidisciplinary rounds. SBRT can be considered for unresectable disease when alternative therapies have failed or are contraindicated. • Liver SBRT is currently under investigation in Phase II clinical trials open at the TBCC and CCI. Consider referral of patients with good liver function (Child Pugh A, B) and a limited number of metastases of an amenable size for participation in these studies. • Continued clinical trials in the use of liver SBRT are recommended. Enrollment of patients into clinical trials or investigational protocols should be encouraged.

Appendix B - Synchronous Metastatic Rectal Cancer Paradigm

Emerging evidence suggests that it may be important to consider the following approaches to potentially resectable metastatic disease, especially for rectal cancer.

Synchronous Metastatic Rectal Cancer⁷⁷



*LAR/APR: low anterior resection/ abdominoperineal resection

Appendix C: Proximal vs. Distal Colorectal Cancer

Criteria	Proximal (Right) Colon	Distal (Left) Colon
Embryologic origin	Arises from midgut <ul style="list-style-type: none"> • Cecum and appendix • Ascending colon • Proximal half to two-thirds of transverse colon 	Arises from hindgut <ul style="list-style-type: none"> • Distal half to one-third of transverse colon • Descending and sigmoid colon • Rectum
Arterial supply	Supplied by superior mesenteric artery	Supplied by inferior mesenteric artery
Incidence	Proximal Primary Tumor Location Less frequent than distal tumor location More likely to occur in females	Distal Primary Tumor Location More frequent than proximal tumor location More likely to occur in males
Presentation	Typically presents with higher TNM stage Often bulky, exophytic, and polypoid Greater chance of mucinous histology	Typically presents with lower TNM stage Often infiltrating and circumferential
Genetics	More frequent microsatellite instability Common site for colorectal cancer in <i>MUTYH</i> -associated polyposis (MAP)	More frequent chromosomal instability Common site for colorectal cancer in familial adenomatous polyposis (FAP)
Immunology	More immunologically active	Less immunologically active
Molecular pathways	Activating mutations of RAS, BRAF, and PIK3CA genes	Gene expression profile corresponding to activation of EGFR

Development and Revision History

This guideline was reviewed and endorsed by the Alberta GI Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, gastroenterologist, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist 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 2010.

Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

HPV, Human Papilloma Virus; HIV, Human Immunodeficiency Virus; CT, Computerized Tomography; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; RT, Radiotherapy; OS, Overall Survival; HR, Hazard Ratio; RFA, radiofrequency ablation; FAP, Familial Adenomatous Polyposis; CI, Confidence Interval; CVC Central Venous Catheter; PICC, Peripherally inserted central catheter; EGFR, Epidermal Growth Factor Receptor; OR, Odds Ratio.

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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