Guideline Resource Unit
guru@ahs.ca

Metastatic Colorectal Cancer

Effective Date: April 2023

Cancer Care Alberta

Clinical Practice Guideline GI-003 – Version 13
www.ahs.ca/guru

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 percent.[1-3] In addition, cytoreductive surgery ("peritoneal stripping") and heated intra-peritoneal chemotherapy may be considered for limited intra-peritoneal metastases.[4] Such treatments require involvement of a multidisciplinary team that should include a hepatobiliary surgeon, thoracic surgeon, and surgical oncologist (see Appendix A). 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 Guidelines[5]

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.

Stereotactic body radiation (SBRT), radiofrequency ablation (RFA)[6] 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) or endoscopic procedure (e.g. stent placement) be considered to relieve or prevent a bowel obstruction. Tumor resection or palliative radiation may be considered for bleeding. Surgery is not recommended for patients 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.

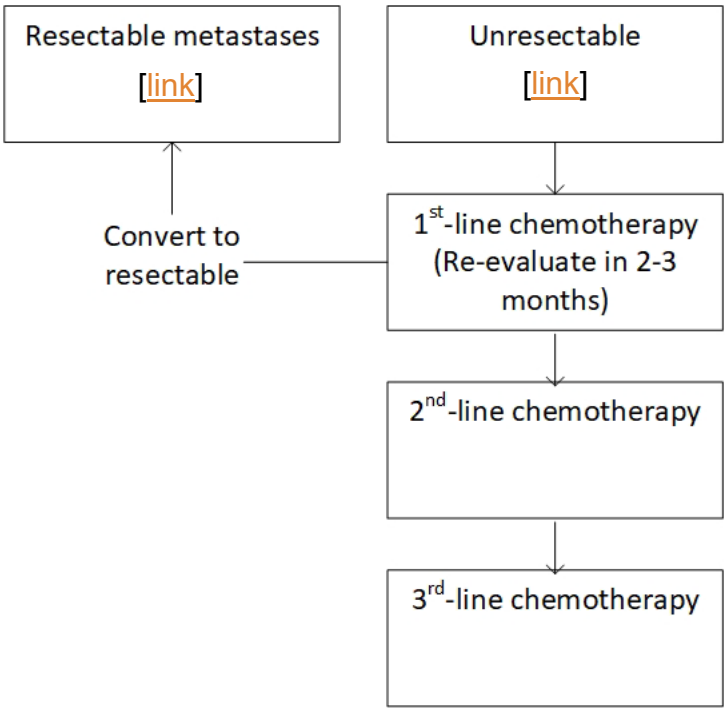


Figure 1. Algorithm for Metastatic Colorectal Cancer Treatment
Multidisciplinary discussion is encouraged. Resection may require multiple procedures. Liver resection may require portal vein embolization. SBRT may be considered.

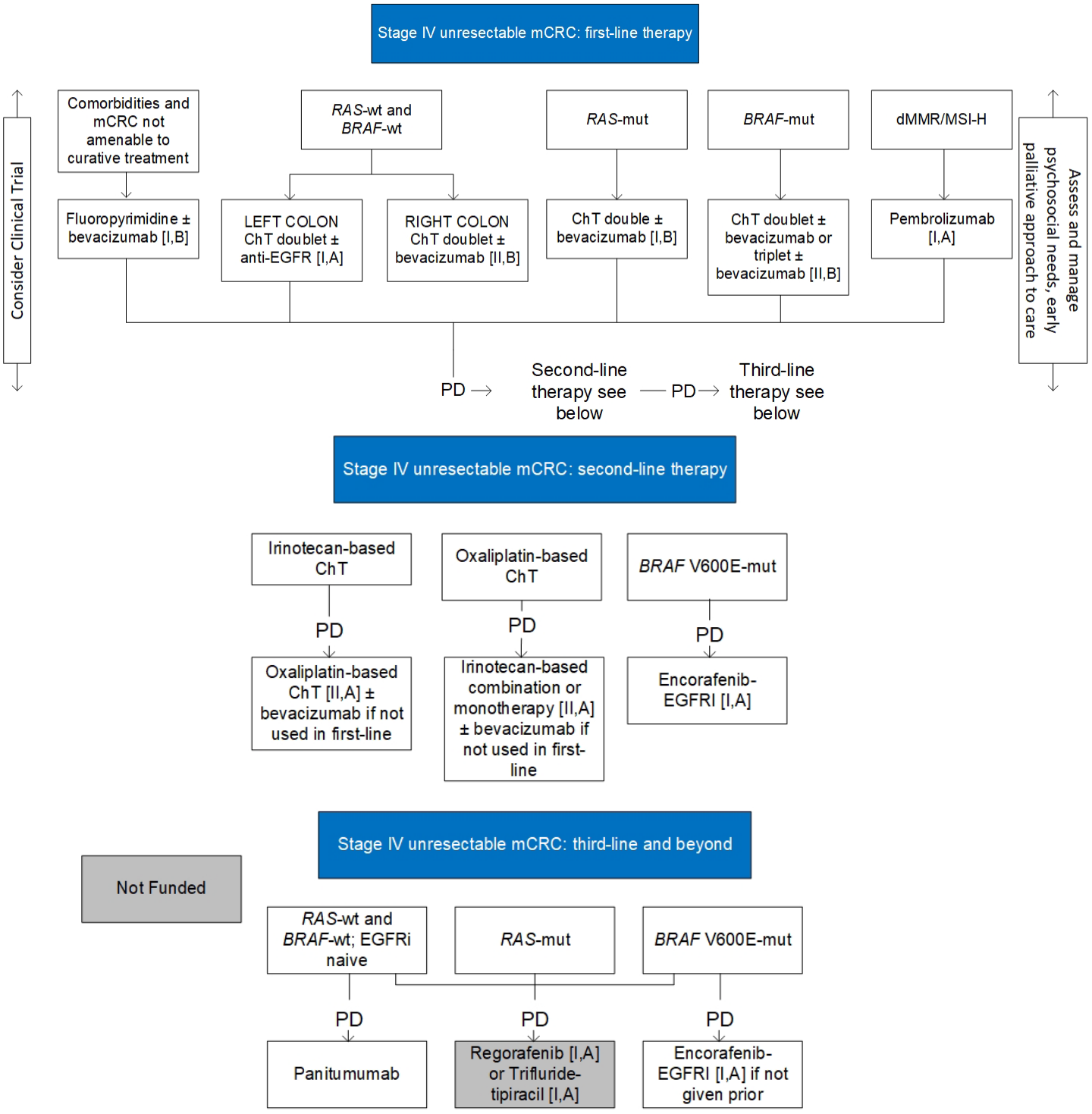


Figure 2. Chemotherapy options for Unresectable Metastatic Colorectal Cancer Consider an Early Palliative Approach to Care, More information. Levels of evidence in square brackets defined here.

5. Standard palliative chemotherapy regimens to consider are described in Table 2.

6. Patients who present with resectable lung or liver metastasis should be discussed in multidisciplinary rounds (Refer to Appendix A). 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%.[20] The addition of cetuximab to FOLFOX in this setting is not appropriate. For patients who have resection of liver metastases with no residual disease, the role of adjuvant chemotherapy is unclear. Post-operative oxaliplatin based chemotherapy for 6 months improved disease-free survival HR 0.67, 95% CI (0.50-0.92, one sided p = 0.006) but not overall survival HR 1.25 (0.78-2.00) two sided P=0.42 in JCOG 0603.[41]
7. 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 sites:[8]
8. The PARADIGM trial demonstrated the superiority of panitumab versus bevacizumab in combination with FOLFOX in patients with left sided, advanced RAS wild type colorectal cancer (median OS 37.9 vs 34.3 months, HR = 0.82, 95.798% CI 0.68-0.99, p = 0.031).[9] Pooled retrospective analyses establish the predictive and prognostic value of primary tumor site using Cetuximab and Panitumumab.[10, 11] 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).[12] The Alberta Provincial Gastrointestinal Tumour Team supports the use of EGFR inhibitors in first-line treatment for patients with *Ras* wild-type, MSS/MMR proficient metastatic colorectal cancer (i.e. non-mutated *Kras* or *Nras*) with left sided primary tumors. 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.).
9. Mutations in *Kras* and *Nras* predict a lack of response in anti-Epidermal Growth Factor Receptor (EGFR) therapy in patients with metastatic colorectal cancer.[13] 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 prolongs progression-free survival compared to best supportive care [Level I Evidence].[14, 15] 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.

10. 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 + bevacizumab.[16] 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 [Level I]. Patients had progressed on 1 or 2 prior treatments.[17] 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 arm.[17] In Alberta, encorafenib is administered with panitumumab. pERC and clinical experts noted that concurrent administration with panitumumab instead of cetuximab would lead to less frequent chemotherapy sessions, and it is expected that patients who receive encorafenib in combination with panitumumab would respond similarly to patients treated with cetuximab.

11. 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
12. For patients with MSI-high or dMMR metastatic colorectal cancer (approximately 3.5% of cases[18]), 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 life [Level I].[19] 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.
13. See Appendix A: "Approach to Metastatic Colorectal Cancer".

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

Regimen	Details
FOLFIRI[12]	• Involves the administration of Irinotecan (180 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an IV infusion of 2,400 mg/m^2 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/m^2 IV over ninety minutes followed by Capecitabine 800 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle).[24] • 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 FOLFIRI.[25] • Due to Oxaliplatin's propensity to cause a cumulative peripheral sensory neuropathy, consider a non–Oxaliplatin-containing regimen before an Oxaliplatin-based regimen. 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 • **Gilbert's syndrome** results from impaired activity of uridine diphosphate glucuronyl-

Regimen	Details
	transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of Irinotecan and thereby increases the risk of severe toxicity.
CAPOX and mFOLFOX6 [12-14]	• **CAPOX** involves the administration of Oxaliplatin (130 mg/m^2 IV over two hours) and Capecitabine 1,000 mg/m^2 PO Q12h for fourteen days in every twenty-one day cycle. • **mFOLFOX6** involves the administration of Oxaliplatin (85 mg/m^2 IV) and Leucovorin (400 mg/m^2 IV) concurrently over two hours followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an intravenous infusion of 2,400 mg/m^2 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 FOLFIRI.[25] • 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]	• Involves the administration of a 90 minute infusion of Irinotecan (165 mg/m^2), a 120 minute infusion of Oxaliplatin (85 mg/m^2), and a concomitant 120 minute infusion of Leucovorin (400 mg/m^2), followed by a 48-hour continuous infusion 5-Fluorouracil (total dose 3200 mg/m^2) 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 toxicity.[16]
Capecitabine[16]	• Involves the administration of Capecitabine 1,250 mg/m^2 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]	• Involves the administration of Irinotecan (350 mg/m^2 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. • 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 • **Gilbert's syndrome** results from impaired activity of uridine diphosphate glucuronyl-transferase isoform 1A1 (UGT_{1A1}). It delays the metabolism of Irinotecan and thereby increases the risk of severe toxicity.
5-Fluorouracil (simplified LV5FU2)	• Involves the administration of Leucovorin (400 mg/m^2 IV over two hours) followed by 5-Fluorouracil (400 mg/m^2 IV bolus and then an intravenous infusion of 2,400 mg/m^2 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).

<table>
<tr><th>Regimen</th><th>Details</th></tr>
<tr><td></td><td>• Supplement with Bevacizumab, where appropriate (see below).</td></tr>
<tr><td>Raltitrexed[18]</td><td>• 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>
<tr><th>Creatinine Clearance</th><th>Dose as Percentage of 3 mg/m^2</th><th>Interval</th></tr>
<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>
</table></td></tr>
<tr><td>Bevacizumab[16, 19-23]</td><td>• 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:
· 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>
<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>
<tr><td>Arterial Thromboembolic Events[26]
Cardiac Ischemia
Cerebrovascular Ischemia</td><td>3.3%</td><td>2.0%
1.5%
1.2%</td><td>HR 2.08</td><td>HR 1.29
HR 2.14
HR 1.37</td></tr>
<tr><td>Proteinuria[27]</td><td>—</td><td>1.0%</td><td>HR 1.40</td><td>—</td></tr>
<tr><td>Hypertension[27]</td><td>—</td><td>8.7%</td><td>—</td><td>HR 3.00</td></tr>
<tr><td>Wound Healing Complications[28-30]</td><td>4.9%</td><td>3.7%</td><td>—</td><td>—</td></tr>
<tr><td>Gastrointestinal Perforation[31]</td><td>—</td><td>0.9%</td><td>—</td><td>HR 2.15</td></tr>
</table>
• Discrepant results exist as to the risk of venous thromboembolic events[32, 33]
• 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.
• Refer to the Bevacizumab Administration Guidelines.</td></tr>
</table>

Regimen	Details
EGFR inhibitor and chemotherapy[13, 34, 35]	• First-line anti-EGFR therapies may include: a. Cetuximab with FOLFIRI[34] b. Panitumumab with FOLFOX[13] c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)[35] • EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome.[36, 37] • 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.38 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 Program.[38]

References

1. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clinical Epidemiology*. 2012;4:283-301.
2. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Annals of Surgery*. 1999;230(3):309-318.
3. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. *Annals of Thoracic Surgery*. 2007;84(1):324-338.
4. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *Journal of Clinical Oncology*. 2003;21(20):3737-3743.
5. Desch CE, Benson AB, 3rd, Somerfield MR, Flynn PJ, Krause C, Loprinzi CL, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. *Journal of Clinical Oncology*. 2005;23(33):8512-8519.

6. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. *Journal of Clinical Oncology*. 2005;23(7):1358-1364.
7. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. *JAMA oncology*. 2017;3(2):211-219.
8. Lee GH, Malietzis G, Askari A, Bernardo D, Al-Hassi HO, Clark SK. Is right-sided colon cancer different to left-sided colorectal cancer? - a systematic review. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2015;41(3):300-308.
9. Yoshino T, Watanabe J, Shitara K, Yasui H, Ohori H, Shiozawa M, et al. Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. meeting-report. *J Clin Oncol*. 2022-06-08 2022;40(17_suppl)
10. Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(8):1862-1868.
11. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. *JAMA oncology*. 2017;3(2):194-201.
12. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(8):1713-1729.
13. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *The New England journal of medicine*. 2013;369(11):1023-1034.
14. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *Journal of Clinical Oncology*. 2007;25(13):1658-1664.
15. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *Journal of Clinical Oncology*. 2008;26(10):1626-1634.
16. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *The LancetOncology*. 2015;16(13):1306-1315.
17. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *The New England journal of medicine*. 2019;381(17):1632-1643.
18. Koopman M, Kortman G, Mekenkamp L, Ligtenberg M, Hoogerbrugge N, Antonini N, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *British journal of cancer*. 01/27/2009 2009;100(2)
19. Diaz L, Shiu K, Kim T, Jensen B, Jensen L, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *The Lancet Oncology*. 2022 May 2022;23(5)
20. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet (London, England)*. 2008;371(9617):1007-1016.
21. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *Journal of Clinical Oncology*. 2006;24(13):2065-2072.
22. Ye L, Liu T, Ren L, Wei Y, Zhu D, Zai S, et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 06/01/2013 2013;31(16)
23. Tang W, Ren L, Liu T, Ye Q, Wei Y, He G, et al. Bevacizumab Plus mFOLFOX6 Versus mFOLFOX6 Alone as First-Line Treatment for RAS Mutant Unresectable Colorectal Liver-Limited Metastases: The BECOME Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 09/20/2020 2020;38(27)

24. Xu R, Muro K, Morita S, Iwasa S, Han S, Wang W, et al. Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randomised, non-inferiority, phase 3 trial. *The Lancet Oncology*. 2018 May 2018;19(5)
25. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *Journal of Clinical Oncology*. 2004;22(2):229-237.
26. Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. *Acta Oncologica*. 2010;49(3):287-297.
27. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. *American Journal of Kidney Diseases*. 2007;49(2):186-193.
28. Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Colangelo LH, Lopa SH, et al. Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. *Journal of Clinical Oncology*. 2009;27(20):3385-3390.
29. Bose D, Meric-Bernstam F, Hofstetter W, Reardon DA, Flaherty KT, Ellis LM. Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care. *Lancet Oncology*. 2010;11(4):373-382.
30. Okines A, Puerto OD, Cunningham D, Chau I, Van Cutsem E, Saltz L, et al. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *British journal of cancer*. 2009;101(7):1033-1038.
31. Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *Lancet Oncology*. 2009;10(6):559-568.
32. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*. 2008;300(19):2277-2285.
33. Hurwitz HI, Saltz LB, Van Cutsem E, Cassidy J, Wiedemann J, Sirzen F, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. *Journal of Clinical Oncology*. 2011;29(13):1757-1764.
34. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *The New England journal of medicine*. 2009;360(14):1408-1417.
35. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(31):4706-4713.
36. Saltz L, Badarinath S, Dakhil S, Bienvenu B, Harker WG, Birchfield G, et al. Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOLFOX-bevacizumab in colorectal cancer. *Clinical colorectal cancer*. 2012;11(2):101-111.
37. Tol J, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *The New England journal of medicine*. 2009;360(6):563-572.
38. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *The New England journal of medicine*. 2015;372(20):1909-1919.
39. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2023 Jan 2023;34(1)
40. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *The LancetOncology*. 2013;14(12):1208-1215.
41. Kanemitsu Y, Shimizu Y, Mizusawa J, Inaba Y, Hamaguchi T, Shida D, et al. Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 12/01/2021 2021;39(34)
42. Bridgewater J, Pugh S, Maishman T, Eminton Z, Mellor J, Whitehead A, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *The Lancet Oncology*. 2020 Mar 2020;21(3)

43. Parikh AA, Gentner B, Wu TT, Curley SA, Ellis LM, Vauthey JN. Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy. *Journal of Gastrointestinal Surgery*. 2003;7(8):1082-1088.
44. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Annals of Surgery*. 2004;240(6):1052-1061.
45. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Annals of Surgery*. 2006;243(1):1-7.
46. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *British Journal of Surgery*. 2007;94(3):274-286.
47. Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Annals of Surgery*. 2008;247(1):118-124.
48. Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer*. 2007;110(12):2761-2767.
49. Zorzi D, Chun YS, Madoff DC, Abdalla EK, Vauthey JN. Chemotherapy with bevacizumab does not affect liver regeneration after portal vein embolization in the treatment of colorectal liver metastases. *Annals of Surgical Oncology*. 2008;15(10):2765-2772.
50. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Annals of Surgery*. 2004;240(4):644-657.
51. Blazer DG, 3rd, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *Journal of Clinical Oncology*. 2008;26(33):5344-5351.
52. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. *Annals of Surgery*. 2004;240(6):1037-1049.
53. Andre TBCM-BLNMTJHTTCZMCPBJT-FIdG. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *New England Journal of Medicine*. 2004;350(23):2343-2351.
54. Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *Journal of Clinical Oncology*. 2007;25(16):2198-2204.
55. Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. *Journal of Clinical Oncology*. 2007;25(23):3456-3461.
56. van Cutsem E, Labianca R, Hossfeld D, Bodoky G, Roth A, Aranda E, et al. Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA (F) in stage III colon cancer patients (pts). (PETACC 3). *J Clin Oncol 2005 ASCO Annual Meeting Proceedings*. 2005;23(16S; abstract LBA8)
57. Ychou M, Raoul J, Douillard J, Bugat R, Mineur L, Viret F, et al. A phase III randomized trial of LV5FU2+CPT-11 vs. LV5FU2 alone in adjuvant high risk colon cancer (FNCLCC Accord02/FFCD9802). *J Clin Oncol 2005 ASCO Annual Meeting Proceedings*. 2005;23(16S; abstract 3502)
58. Portier G, Elias D, Bouche O, Rougier P, Bosset JF, Saric J, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial. *Journal of Clinical Oncology*. 2006;24(31):4976-4982.
59. Park IJ, Kim HC, Yu CS, Kim PN, Won HJ, Kim JC. Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery. *Annals of Surgical Oncology*. 2008;15(1):227-232.
60. Lee WS, Yun SH, Chun HK, Lee WY, Kim SJ, Choi SH, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. *Journal of clinical gastroenterology*. 2008;42(8):945-949.
61. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Annals of Surgery*. 2004;239(6):818-825.
62. Sugarbaker PH. Peritonectomy procedures. *Annals of Surgery*. 1995;221(1):29-42.
63. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer treatment reviews*. 2001;27(6):365-374.

64. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *Journal of Clinical Oncology*. 2004;22(16):3284-3292.
65. Kanemitsu Y, Shitara K, Mizusawa J, Hamaguchi T, Shida D, Komori K, et al. Primary Tumor Resection Plus Chemotherapy Versus Chemotherapy Alone for Colorectal Cancer Patients With Asymptomatic, Synchronous Unresectable Metastases (JCOG1007; iPACS): A Randomized Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 04/01/2021 2021;39(10)
66. Rahbari N, Lordick F, Fink C, Bork U, Stange A, Jäger D, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555). *BMC cancer*. 04/05/2012 2012;12
67. Vautravers-Dewas C, Dewas S, Bonodeau F, Adenis A, Lacornerie T, Penel N, et al. Image-guided robotic stereotactic body radiation therapy for liver metastases: is there a dose response relationship? *International journal of radiation oncology, biology, physics*. 2011;81(3):39.
68. Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. *Cancer*. 2011;117(17):4060-9.
69. Kress MAS, Collins BT, Collins SP, Dritschilo A, Gagnon G, Unger K. Stereotactic body radiation therapy for liver metastases from colorectal cancer: Analysis of safety, feasibility, and early outcomes. *Frontiers in Oncology*. 2012;2
70. Stintzing S, Hoffmann RT, Heinemann V, Kufeld M, Muacevic A. Frameless single-session robotic radiosurgery of liver metastases in colorectal cancer patients. *European journal of cancer (Oxford, England : 1990)*. 2010;46(6):1026-1032.
71. van der Pool AE, Mendez Romero A, Wunderink W, Heijmen BJ, Levendag PC, Verhoef C, et al. Stereotactic body radiation therapy for colorectal liver metastases. *The British journal of surgery*. 2010;97(3):377-382.
72. Wulf J, Guckenberger M, Haedinger U, Oppitz U, Mueller G, Baier K, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. *Acta Oncologica (Stockholm, Sweden)*. 2006;45(7):838-847.
73. Yamashita H, Onishi H, Matsumoto Y, Murakami N, Matsuo Y, Nomiya T, et al. Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. United Kingdom: BioMed Central Ltd; 2014.
74. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *British Journal of Surgery*. 2006;93(7):872-878.

Appendix A: Approach to Metastatic Colorectal Cancer

<table>
<tr>
<td>Resectable lung or liver metastases</td>
<td>

Consider upfront resection especially for patients with favorable criteria: metachronous, fewer lesions, unilobar disease, no extra-hepatic disease.[39]

Perioperative oxaliplatin based chemotherapy, with 3 months pre-hepatic resection and 3 months post-hepatic resection can be considered for patients with resectable liver metastases, especially when the prognosis is unclear. This strategy improved three-year progression-free survival (423.4% versus 33.2% in resected patients, HR=0.73;95%CI: 0.55-0.97; p=00.025) in EORTC 40983, however, overall survival was not improved (Level II).[20, 40]
The optimal role of adjuvant chemotherapy after upfront resection is unclear. Post-operative oxaliplatin based chemotherapy for 6 months improved disease-free survival HR 0.67, 95% CI (0.50-0.92, one sided p = 0.006) but not overall survival HR 1.25 (0.78-2.00) two sided P=0.42.[41]

The use of chemotherapy in this setting may be influenced by the clinical presentation: synchronous versus metachronous presentation, technical criteria for resectability, and/or number and size of metastases.[39]
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 R_0 and 0% for R_1 or R_2 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 outcome.[2]
<table>
<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>
<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>
</table>
The definition of resectable liver metastases continues to evolve. Currently, resection is considered possible if both an R_0 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 volume.[38] 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).[42]

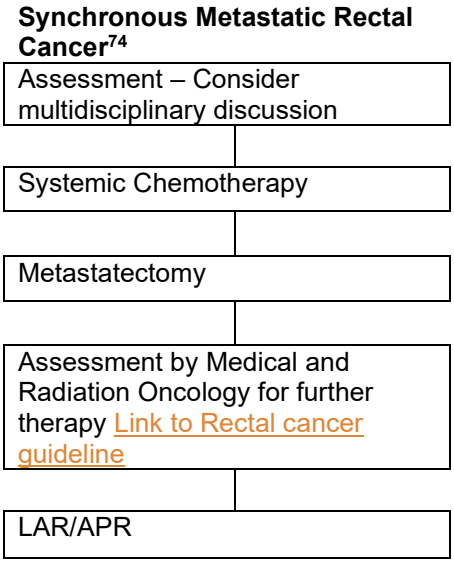
</td>
</tr>
</table>

Marginally resectable liver metastases	• 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% *versus* 33.2% in resected patients, HR 0.73, $CI_{95\%}$ 0.55-0.97, $p = 0.025$).[20] • 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. The general approach for consideration of a biologic agent for non-liver limited mCRC should be used. Kras wild type, left sided primary, consider panitumumab;[22] Kras mutant, consider bevacizumab.[23] • 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 delivered.[45] The type of hepatic injury is regimen specific:[46] · 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% *versus* 14.7%, $p = 0.001$).[21] · Oxaliplatin predisposes to sinusoidal obstruction (characterized by peri-sinusoidal inflammation, congestion, fibrosis, and venous occlusion). Some studies[21] suggest that it fails to increase the risk of peri-operative death while others[47] suggest that it increases morbidity (from 6.3% to 40.0%, $p < 0.026$) and prolongs length-of-stay (from 10.9 days to 17.0 days, $p < 0.006$) 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%, $p < 0.01$) as well as the degree of tumor viability when used in combination with 5-Fluorouracil and Leucovorin (32.9% *versus* 45.3%, $p = 0.02$).[48] Bevacizumab fails to impair liver regeneration after portal vein embolization.[49] • In a retrospective analysis of patients with initially unresectable metastatic disease,[50] 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 Bevacizumab.[51] • 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 embolization.[52] • The addition of Oxaliplatin[53, 54] but not Irinotecan[55-57] 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]
Radiofrequency ablation [Level II]	• 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 studies[59-61] 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.
Peritoneal carcinomatosis	• 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

	(median survival 22.3 months *versus* 12.6 months, HR 0.55, $CI_{95\%}$ 0.32-0.95, p = 0.032).[4] 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 (R_1) confers a significantly superior survival than patients with residual disease (R_2). • Cytoreductive surgery[62] 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 metabolism[64]. Hyperthermia is synergistic with cytotoxic agents.[63] The process is associated with a reported morbidity and mortality rates of 22.9% and 4%, respectively.[64]
Unresectable disease	• 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.[65, 66] Obstruction and bleeding complicate only 13.9% and 3.0% of cases treated with palliative chemotherapy when the primary tumor is left *in situ*. 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) [Level III]	• 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 studies.[67-73] • 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.



*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*** • Cecum and appendix • Ascending colon • Proximal half to two-thirds of transverse colon	Arises from ***hindgut*** • 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 *MUTYH*-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 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 2010.

Levels of Evidence

I	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
II	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
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	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

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.

Funding Source

Financial support for the development of CancerCare Alberta's evidence-based clinical practice guidelines and supporting materials comes from the CancerCare Alberta operating budget; no outside commercial funding was received to support the development of this document.

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*.

Conflict of Interest Statements

Dr. Oliver Bathe has nothing to disclose.
Dr. Jay Easaw reports honoraria from LEO, Elvium, and Amgen.
Dr. Richard Lee-Ying reports grants from Sanofi, and other support from Jansen, Roche, Celgene, and Taiho.
Dr. Safiya Karim reports personal fees from Amgen and Taiho, and is on advisory boards for Bristol-Myers Squibb and Sanofi.
Dr. Andrew Scarfe has nothing to disclose.
Dr. Patricia Tang reports grants from Pfizer and Roche, and other support from Amgen, Taiho, AstraZeneca, and Genomic Health.
Derek Tilley has nothing to disclose.

Citation

Tang P (lead), Bathe O, Easaw J, Lee-Ying R, Karim S, Scarfe A, Tilley D. Cancer Care Alberta, Alberta Health Services (2022). Clinical Practice Guideline on [Metastatic Colorectal Cancer, Version 13]. Accessed [Month, Year]. Available from: www.ahs.ca/guru