Metastatic Colorectal Cancer

Effective Date: April, 2020
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). 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):

<table>
<thead>
<tr>
<th>Post-Metastatectomy Colorectal Cancer Surveillance Guidelines(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If resection of another recurrence from liver and/or lung is clinically appropriate,</td>
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<tr>
<td>• Obtain a CEA every three months for five years (progressive rises warrant a workup for recurrent disease); and</td>
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<tr>
<td>• Obtain a CT scan of the thorax, abdomen, and pelvis at the discretion of the treating physician.</td>
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</tbody>
</table>

Radiofrequency ablation\(^6\) (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 \textit{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. 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.

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active and able to carry on without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care and/or confined to a bed or chair for more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.</td>
</tr>
</tbody>
</table>

3. 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 (versus proximal) colon is
associated with a better survival (HR 0.82, CI₉₅% 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. When the CALGB/SWOG 80405 trial is analyzed retrospectively based upon site of the primary tumor, a median overall survival of 33.3 months is achieved when the primary tumor originates in the distal colon; it is 19.4 months when the primary tumor originate in the proximal colon (HR 1.55, CI₉₅% 1.32-1.82, p < 0.001). In patients who received Cetuximab as a component of their first-line therapy (with FOLFOX or FOLFIRI), a median overall survival of 36.0 months is achieved if the primary tumor originated in the distal colon versus 16.7 months for a primary tumor originating in the proximal colon (HR 1.87, CI₉₅% 1.48-2.32, p < 0.001). In patients who received Bevacizumab as a component of their first-line therapy (with FOLFOX or FOLFIRI), a median overall survival of 31.4 months is achieved if the primary tumor originated in the distal colon versus 24.2 months for a primary tumor originating in the proximal colon (HR 1.32, CI₉₅% 1.05-1.65, p = 0.01).

Pooled retrospective analyses establish the predictive and prognostic value of primary tumor site using Cetuximab and Panitumumab⁹,¹⁰. 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, treatment policies, 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. Therefore, primary tumor location ("sidedness") appears to represent a surrogate for the complex but as yet only partially understood biology. 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.).

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

5. Patients with metastatic colorectal cancer should receive testing for activating mutations of Ras (Kras and Nras) in tumour tissue at diagnosis of stage IV disease. Douillard et al. found that Ras mutations 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.
Cetuximab administered as a 400 mg/m² IV loading dose followed by 250 mg/m² IV weekly maintenance prolongs median overall survival from 4.8 months to 9.5 months ($p < 0.0001$, HR 0.55, CI95% 0.41-0.74)\textsuperscript{32,33}. Panitumumab administered at 6 mg/kg IV over sixty minutes every two weeks prolongs progression-free survival\textsuperscript{34,35}. Panitumumab is funded for patients with \textit{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. \textit{Kras} regulates this cascade. The \textit{Kras} gene may be “wild-type” (in up to 65% of cases) or “mutated”. Wild-type \textit{Kras} remains active only transiently after interaction of EGFR with its ligand. Mutated \textit{Kras} remains constitutively activate 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”) \textit{Kras} would not be influenced by such therapy. \textit{Kras} testing by quantitative PCR (or direct DNA sequencing) is highly specific for mutations known to confer constitutive activation.

6. The Alberta Provincial Gastrointestinal Tumour Team supports the use of EGFR inhibitors in first-line treatment for patients with \textit{Ras} wild-type metastatic colorectal cancer (i.e. non-mutated \textit{Kras} or \textit{Nras}) with left sided primary tumors.

7. Patients with \textit{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. There is a paucity of research in this area to guide optimal upfront treatment. The TRIBE trial was a phase III open label randomized patients with metastatic colorectal cancer to either FOLFOXIRI + bevacizumab or FOLFIRI + bevacizumab\textsuperscript{15}. Of the 508 patients in this study, 28 patients with \textit{BRAFV600E} mutations were enrolled, of whom 12 patients were assigned to the FOLFIRI bevacizumab arm and 16 patients were assigned to the FOLFOXIRI bevacizumab arm. Across both arms, the median OS in the RAS-and \textit{BRAF}-wild-type patients was 37.1 vs 13.4 months in the small subset of patients with tumors harboring \textit{BRAFV600E} mutations (HR 2.79; 95% CI 1.75–4.46; $P<0.0001$). Although the number of patients with \textit{BRAFV600E} mutations in this study was small, the median OS of patients treated with FOLFOXIRI plus bevacizumab in TRIBE was 19.0 months compared to 10.7 months in the FOLFIRI plus bevacizumab arm (HR 0.54; 95% CI 0.24–1.20). An overall response was reported in 56% of patients with a \textit{BRAFV600E} mutation receiving FOLFOXIRI plus bevacizumab vs 42% of patients receiving FOLFIRI plus bevacizumab (odds ratio [OR] 1.82, 95% CI 0.91–2.62). A small single arm phase II trial also evaluating the triplet regimen plus bevacizumab as upfront treatment for \textit{BRAF} mutant patients showed a mPFS of 11.8 months and mOS of 24.1 months\textsuperscript{36}. Overall RR was 72%. Therefore for patients with good
performance status, a triplet regimen of FOLFOXIRI + bevacizumab can 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 treatments. 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 again the standard treatment arm. The median overall survival of the triplet regimen was 9 months vs. 5.2 months for the standard treatment (HR 0.52, 95% CI 0.39-0.70, p<0.001). The response rate was 26% (95% CI, 18 to 35) in the triplet-therapy group and 2% (95% CI, 0 to 7) in the control group (P<0.001). The overall survival in the doublet therapy group was 8.4 months (HR 0.60, 95% CI 0.45-0.79, p<0.001). In a descriptive analysis of survival comparing the triplet regimen with the doublet regimen, the estimated 6-month survival was 71% in the triplet-therapy group and 65% in the doublet-therapy group (hazard ratio for death, 0.79; 95% CI, 0.59 to 1.06). 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 regimen.

8. 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

9. 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 therapy. See Appendix: “Approach to Metastatic Colorectal Cancer.”

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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
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</table>
| FOLFIRI  | • 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 |
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
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|                 | 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). 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. 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-transferase isoform 1A1 (UGT1A1). It delays the metabolism of Irinotecan and thereby increases the risk of severe toxicity. |
| CAPOX and FOLFOX 12-14 | 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. FOLFOX involves the administration of Oxaliplatin (100 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 FOLFIRI. 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/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. |
Regimen | Details
---|---
| as the progression free survival and overall survival improvement associated with FOLFOXIRI and Bevacizumab in the TRIBE study were accompanied with increased toxicity. |
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).  
• Supplement with Bevacizumab, where appropriate (see below). |
Raltitrexed\(^{18}\) | • 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>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dose as Percentage of 3 mg/m(^2)</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 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>&lt; 25 mL/minute</td>
<td>No therapy</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Bevacizumab\(^1\)\(^{6,19-23}\) | • 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;
<table>
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<tr>
<th>Regimen</th>
<th>Details</th>
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<tr>
<td>• Uncontrolled hypertension;</td>
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<tr>
<td>• 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);</td>
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<tr>
<td>• Inherited bleeding diathesis, coagulopathy, or esophageal varices;</td>
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<td>• Significant proteinuria or renal dysfunction;</td>
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<tr>
<td>• Non-healing wound, ulcer, or bone fracture;</td>
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<tr>
<td>• Metastases within central nervous system or ophthalmologic abnormalities; and</td>
<td></td>
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<tr>
<td>• Pregnancy, lactation, or childbearing potential without effective contraception.</td>
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• 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 (Q2 week chemotherapy schedule) or over fifteen minutes at 7.5 mg/kg IV (Q3 week chemotherapy schedule).

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Summary Incidence</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial Thromboembolic Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Ischemia</td>
<td>3.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Cerebrovascular Ischemia</td>
<td>1.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>—</td>
<td>1.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>—</td>
<td>8.7%</td>
</tr>
<tr>
<td>Wound Healing Complications</td>
<td>4.9%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>—</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

• Discrepanent results exist as to the risk of venous thromboembolic events²³,²⁶
• 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.
• Refer to the Bevacizumab Administration Guidelines.

EGFR inhibitor and chemotherapy²⁷-²⁹

• First-line anti-EGFR therapies may include:
  a. Cetuximab with FOLFIRI²⁷
  b. Panitumumab with FOLFOX²⁸
  c. Panitumumab with FOLFIRI (based on extrapolation from data in second-line treatment)²⁹
Regimen | Details
---|---
• EGFR inhibitors should not be given with bevacizumab as clinical trials with combinations of both EGFR inhibitor and bevacizumab give worse outcome\textsuperscript{30,31}.
• Refer to Panitumumab and Cetuximab: Toxicity Management Guidelines

10. 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\textsuperscript{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\textsuperscript{40}.
References


78. Xu RH, Muro K, Morita S, Iwasa S, Han SW, 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 Lancet Oncol 2018; 19(5): 660-671.
Appendix A: Approach to Metastatic Colorectal Cancer

Resectable lung or liver metastases

- 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 survival⁴¹,⁴², 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>
<thead>
<tr>
<th>“Fong Score”</th>
<th>Survival One-Year</th>
<th>Survival Two-Year</th>
<th>Survival Three-Year</th>
<th>Survival Four-Year</th>
<th>Survival 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>

- 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.
**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, \(p = 0.025\))\(^{41}\).
- 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.
- Although the addition of anti-EGFR therapy to chemotherapy often improves response rates in patients with Kras wild-type disease, such therapy was associated with an inferior progression-free survival in a study presented at ASCO 2013 (Abstract 3504).
- 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%, \(p = 0.001\))\(^{39}\).
  - Oxaliplatin predisposes to sinusoidal obstruction (characterized by peri-sinusoidal inflammation, congestion, fibrosis, and venous occlusion). Some studies\(^{39}\) 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 \(\leq 5\) µg/L, tumor size \(\leq 3\) 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**

- 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.
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).

- Cytoreductive surgery involves the complete removal of macroscopic disease (e.g.: peritoneectomy, omentectomy, cholecystectomy, splenectomy, abdominal organs involved with tumor), lysis of intra-abdominal adhesions (to permit optimal exposure to heated intraperitoneal 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. Hyperthermia is synergistic with cytotoxic agents. The process is associated with a reported morbidity and mortality rates of 22.9% and 4%, respectively.

### Unresectable disease

- Consider palliative chemotherapy.
- Resection of an asymptomatic primary colorectal cancer provides only minimal palliative benefit, risks morbidity and mortality, and delays initiation of systemic therapy. 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)

- 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.
- 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: Algorithm for the Treatment of Liver Metastasis from Colorectal Cancer

Modified Algorithm for Treatment of Liver Metastasis from Colorectal Cancer

Resectable

Pre-Operative Chemotherapy§ (for two to three months)

(One- or Two-Stage) Hepatic Metastatectomy ± Portal Vein Embolization

Post-Operative Chemotherapy (to complete a total of six months)

Resectable

Unresectable

First-Line Chemotherapy (re-evaluate in two to three months)

Clinical Trial EGFRi + chemotherapy FOLFIRI/OxFp ± Bevacizumab Capecitabine

Second-Line Chemotherapy

Clinical Trial OxFp/FOLFIRI ± Bevacizumab* Irinotecan SBRT**

Third-Line Therapy

Clinical Trial EGFRi OxFp* ➔ EGFRi

Notes:
OxFp = FOLFOX or CAPOX
EGFRi only in Kras wild-type
* if not used in a prior line of therapy

§ The addition of anti-EGFR monoclonal antibody therapy appears to improve the response rates of chemotherapy (and, thereby, may be able to enhance conversion of borderline resectable disease to resectable disease) in patients with Kras wild-type disease.

**SBRT (SBRT=Stereotactic Body Radiotherapy) can be considered when alternative therapies have failed or are contraindicated, or for palliation of symptoms.

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

Encourage the discussion of patients at multidisciplinary rounds.
Traditional Approach

- Assessment
- Chemoradiotherapy or short course radiation therapy
- LAR/APR*
- Systemic Chemotherapy
- Liver Resection

Fifteen weeks without effective systemic therapy

Reverse Approach

- Assessment
- Systemic Chemotherapy
- Liver Resection
- Assessment by Medical and Radiation Oncology for further therapy
- LAR/APR

*LAR/APR: low anterior resection/ abdominoperineal resection
## Appendix C: Proximal vs. Distal Colorectal Cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Proximal (Right) Colon</th>
<th>Distal (Left) Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryologic origin</td>
<td>Arises from <em>midgut</em> • Cecum and appendix • Ascending colon • Proximal half to two-thirds of transverse colon</td>
<td>Arises from <em>hindgut</em> • Distal half to one-third of transverse colon • Descending and sigmoid colon • Rectum</td>
</tr>
<tr>
<td>Arterial supply</td>
<td>Supplied by <em>superior mesenteric artery</em></td>
<td>Supplied by <em>inferior mesenteric artery</em></td>
</tr>
<tr>
<td>Incidence</td>
<td>Proximal Primary Tumor Location Less frequent than distal tumor location More likely to occur in <em>females</em></td>
<td>Distal Primary Tumor Location More frequent than proximal tumor location More likely to occur in males</td>
</tr>
<tr>
<td>Presentation</td>
<td>Typically presents with higher <em>TNM stage</em> Often bulky, exophytic, and polypoid Greater chance of <em>mucinous histology</em></td>
<td>Typically presents with lower TNM stage Often infiltrating and circumferential</td>
</tr>
<tr>
<td>Genetics</td>
<td>More frequent <em>microsatellite instability</em> Common site for colorectal cancer in MUTYH-associated polyposis (MAP)</td>
<td>More frequent <em>chromosomal instability</em> Common site for colorectal cancer in familial adenomatous polyposis (FAP)</td>
</tr>
<tr>
<td>Immunology</td>
<td>More immunologically active</td>
<td>Less immunologically active</td>
</tr>
<tr>
<td>Molecular pathways</td>
<td><em>Activating mutations of RAS, BRAF, and PIK3CA genes</em></td>
<td><em>Gene expression profile corresponding to activation of EGFR</em></td>
</tr>
</tbody>
</table>
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.

Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>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</td>
</tr>
<tr>
<td>II</td>
<td>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</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinion</td>
</tr>
</tbody>
</table>

Strength of Recommendations

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

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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