



Provincial Colorectal Cancer Treatment Guidelines

**As per consensus at the Provincial Colorectal Cancer Meeting, June 17, 2011.
Version 3 February 2019**

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. Saskatchewan Cancer Agency (SCA) disclaims all liability for the use of guidelines except as expressly permitted by SCA. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from SCA.

Recommendations for drug treatment presented in the SCA guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency Drug Formulary on the www.saskcancer.ca website for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

SCREENING

Screening for colorectal cancer (CRC) has shown to decrease the mortality and is strongly advised. Please refer to the Saskatchewan Screening Program for Colorectal Cancer.

WORK UP FOR SUSPICIOUS COLORECTAL MASS

- 1) History and Physical examination
- 2) CBC, metabolic profile and CEA level
- 3) Colonoscopy (A multimodality assessment incorporating both endoscopic and radiographic findings is recommended if there is any question about the location of the tumor in the rectum compared with the sigmoid colon).
- 4) Biopsy & pathology
- 5) Mismatch repair (MMR) testing should be performed in all CRC patients for Lynch syndrome ascertainment and for predictive and prognostic factors.
- 6) Extended RAS and BRAF testing should be performed in patients with metastatic disease being considered for systemic therapy. These results should be available in a reasonable timeframe to facilitate first line chemotherapy selection.
- 7) CT scan of chest, abdomen, and pelvis

- 8) EUS and endorectal coil or pelvic MRI for staging in rectal cancer.
- 9) PET/CT or MRI abdomen as needed, for example, for equivocal staging CT scan or if there is a consideration of metastasectomy.

INTENT OF TREATMENT:

Patients with stage I to III colon and rectal cancer (localized cancer) are treated with the intention of cure.

Patients with unresectable locally advanced disease who achieve good response to systemic and or local therapy and undergo surgery or in selected patients with stage IV colorectal cancer with limited liver and or lung metastases if metastasectomy is an option there is a potential for long-term remission or cure.

LOCALIZED COLON CANCER (Stage I-III)

Surgery

- Complete resection of the tumor including en bloc resection of locally involved tissue or organs in order to achieve clear margins (R0) and removal of local lymph nodes.
- A minimum of 12 lymph nodes examination is required to accurately determine N stage. To ensure this is achieved, it is recommended that the entire mesentery containing the blood supply and lymphatics of the primary feeding named artery (or arteries) to the portion of colon containing the tumor be resected en bloc with this portion of colon.

Adjuvant Chemotherapy

- Stage 1 (T1N0 or T2N0): No adjuvant therapy is recommended.
- Stage 2: T3N0 with MSI-H: Adjuvant therapy can be omitted.
- Stage 2 colon cancer with MSS or MSI-low and with any one of the following poor prognostic features: Consider 6 months of adjuvant therapy with 5-FU/Leucovorin or Capecitabine. FOLFOX or CapeOx may be considered.
 - Note: At present time survival benefit of Oxaliplatin based regimen therapy in stage II patients is not available. Therefore Oxaliplatin-based regimen is not routinely recommended in stage II patients. It can be considered in selected patients younger than 70 yrs of age with multiple high risk factors.
- Poor prognostic features:
 - T4 disease
 - poorly differentiated histology
 - perineural or lymphovascular involvement

- inadequate lymph node sampling (<12 nodes)
 - obstruction or localized perforation
 - close, indeterminate or positive margin
- Stage 3 (T1-4,N+):
 - For T1-3,N1 disease 3 months of CAPOX treatment is a reasonable option. If using FOLFOX, 6 months should remain the standard.
 - In “high risk” Stage III (T4 or N2), 6 months of oxaliplatin based treatment is the standard of care.

Consider using a single agent (5-FU/Leucovorin or Capecitabine) in patients who are not candidate of Oxaliplatin-based combination therapy.

Adjuvant Radiotherapy

- Consider adjuvant radiation therapy for T4 tumors with penetration into fixed adjacent structure (45 to 50.4 Gy in 25 to 28 fractions with or without concurrent 5-FU or Capecitabine) after discussion at multidisciplinary tumor (MDT) rounds.
- At the present time best approach for patients with early stage colon cancer and positive resection margin is not known. Positive margin status should be discussed in MDT rounds regarding role of radiation. Effort should be made by surgeon to mark areas of suspicious margin status.

LOCALIZED RECTAL CANCER (Stage I-III)

Surgery

- Total Mesorectal Excision (TME) with removal of local lymph nodes.
- A minimum of 12 lymph nodes examination is required to accurately determine N stage. This should be achieved through successful TME and ligation of the mesentery as proximal as possible. The 12 lymph node target may not be achieved in some patients who receive neoadjuvant therapy.
- Selected clinical T1N0 lesions can be considered for local excision. High risk factors such as tumor grade, vascular invasion, and sub-mucosal depth of invasion indicate a higher risk of nodal involvement and should be reviewed for consideration of further management. Cases undergoing local excision should undergo multi-disciplinary review. Local excision should occur via TAE (transanal excision), TEMS (Transanal endoscopic microsurgery) or TAMIS (Transanal minimally invasive surgery). These patients will require close follow up involving periodic endoscopy and imaging.

Chemoradiation

- Stage I (T1N0 or T2N0): Surgery alone and no adjuvant therapy is recommended.
- Selected, T2N0, low rectal tumors may be considered for neo-adjuvant concurrent chemo-radiation treatment after MDT consensus for sphincter preservation.
- Stage II (T3N0 or T4N0) & Stage III (T1-4N+):
 - Neoadjuvant chemo radiotherapy: 5-FU or Capecitabine and radiation dose of 45-50.4 Gy in 25 to 28 fractions followed by surgical resection in 6-10 weeks followed by adjuvant chemotherapy with 5-FU or Capecitabine or FOLFOX (total duration of perioperative therapy is 6 months).
 - In patients primary resectable cancer, $\geq T3$ and/or node positive disease, who are not candidates for neoadjuvant chemo radiotherapy, short course of neoadjuvant radiation therapy (25 Gy in 5 fraction) ideally should be considered, followed by surgery in 7-10 days. However delayed surgery 4-8 weeks later can be considered following discussion in the MDT round.
 - If surgery is performed upfront: for $\geq T3$ and/or node positive disease, adjuvant chemoradiotherapy with 5-FU or Capecitabine and radiation followed adjuvant chemotherapy with 5-FU or Capecitabine or FOLFOX (total duration of therapy is 6 months) is recommended.
 - Proximal T3N0 rectal tumors with favorable prognostic feature (refer to unfavorable prognostic features as describe above). Discussion in MDT rounds for neo-adjuvant or adjuvant treatment.
 - If there is a consideration for total neoadjuvant therapy it should be discussed in a MDT round.

LOCALLY ADVANCED UNRESECTABLE COLORECTAL CANCER

- Combination chemotherapy \pm Bevacizumab or Cetuximab/Panitumumab in KRAS wild type tumors (if applicable, left sided tumors only). Both targeted agents have shown higher response when combined with combination chemotherapy. Concurrent chemotherapy with radical radiation or radiation alone in selected cases (RT dose: At least 50.4 to 54Gy in 28-30 fractions).
- Reassessment for conversion to surgical resection every 2 months.
- Consider to hold off on Bevacizumab or Cetuximab/Panitumumab if R0 resection.

UPFRONT RESECTABLE METASTATIC COLORECTAL CANCER (Stage IV)

- For lung or liver metastasis
- Surgery preferred (colectomy, with synchronous or staged liver or lung resection)
- Adjuvant therapy with 6 months of FOLFOX or CapeOx or Capecitabine or 5-FU/Leucovorin
- Alternatively perioperative FOLFOX or CapOx (total duration of treatment for 6 months) may be considered in selected cases.
- Consider incorporating radiation therapy to the primary tumor site (rectal cancer).
- The best sequence of systemic and local therapies including sequencing of surgery is not well defined in patients with resectable or borderline resectable advanced rectal cancer and synchronous liver metastases. For borderline resectable disease upfront systemic therapy is the preferred option.
- Single deposit in lung in the absence of systemic disease could be considered for SBRT if not surgical candidate.

POTENTIALLY RESECTABLE OLOIGOMETASTATIC COLORECTAL CANCER (Stage IV) (CONVERSION THERAPY)

- For Lung and/or Liver or selected peritoneal metastasis
- If conversion is the goal, a regimen leading to high response rate is recommended considering the patient's fitness and motivation. The optimal chemotherapy regimen for conversion therapy is not established. The following regimens can be considered:
 - Cytotoxic triplet (FOLFIXIRI +/- Bevacizumab) (Left or Right sided, EGFR mutant or wild type)
 - Left sided RAS wild Type disease, cytotoxic doublet plus an EGFR antibody (Preferred option)
 - Right sided RAS wild type/any side mutant disease - cytotoxic doublets plus Bevacizumab
- Reassessment for conversion to surgical resection every 2 months.
- Consider incorporating radiation therapy to the primary tumor site (rectal cancer).
- Bevacizumab or Cetuximab/Panitumumab is not recommended following R0 resection.

UNRESECTABLE METASTATIC COLORECTAL CANCER (Stage IV) (Where disease control is the main goal)

- Single agent or combination of chemotherapy ± biologics is the mainstay of treatment.
- Surgery and/or radiation maybe considered for palliation of symptoms.

First line therapy

- In RAS/BRAFV600 wild type LEFT sided colorectal cancer – Cytotoxic doublets plus anti-EGFR agents are the preferred biologics.
- In RIGHT sided wild type or RAS mutant colorectal cancer patients – Cytotoxic doublets plus anti-VEGF agents (Bevacizumab) should be considered in the first line setting
- Patients receiving first line anti-EGFR should also be eligible for second line anti-VEGF unless contra-indicated
- In selected patients after 3 to 6 months of induction therapy, consider a complete chemotherapy break or maintenance therapy with a single agent fluoropyrimidine (infusional 5FU or capecitabine) until progression.
- On disease progression, while on maintenance therapy, re-introduce Induction therapy ± Bevacizumab
- Patients not appropriate for intensive therapies consider: 5-FU or Capecitabine or modified IFL ± Bevacizumab.

Second line therapy

- FOLFOX or Cape OX (if treated with FOLFIRI) or FOLFIRI (if treated with FOLFOX)
- Consider Bevacizumab, if it was not used as first line therapy.
- In selected patients continuation of Bevacizumab beyond progression with a 2nd line fluoropyrimidine-based chemotherapy regimen or alternatively Aflibercept or ramucirumab in combination with 2nd line chemotherapy or in RAS (BRAF)WT anti-EGFR monoclonal antibodies (Cetuximab or Panitumumab) in combination with 2nd line therapy can be considered, if available.
- In selected patients after 3 to 6 months of treatment or if patient develops grade ≥2 neuropathy while on Oxaliplatin consider 5-FU ± Bevacizumab until progression.

- On progression of disease while on maintenance therapy re-introduce second line regimen ± Bevacizumab.
- Bevacizumab alone should not be used in maintenance phase.

Third line therapy

- In RAS and BRAF wild tumors: If previously not received anti-EGFR monoclonal antibodies consider Cetuximab or Panitumumab as single agent or Irinotecan + Cetuximab
- RAS and BRAF mutated tumors: Regorafenib has shown modest benefit and can be considered in patients with good performance status however toxicities are of concern.

Fourth line therapy

- Regorafenib has shown modest benefit and can be considered in patients with good performance status.
- Trifluridine/tipiracil (TAS-102) for patients previously treated with fluoropyrimidines, Oxaliplatin, Irinotecan, biologics (if applicable)
- **Immunotherapy in patients with metastatic colorectal cancer**
 - Use of a PD1 inhibitors (Nivolumab or Pembrolizumab) is a reasonable option in patients with Stage IV MSI-H or MMR deficient colorectal cancer after treatment failure/intolerance to fluoropyrimidine, oxaliplatin and irinotecan. In MMR proficient tumors, single agent Nivolumab or Pembrolizumab have been shown to be ineffective and should not be used.

SURVEILLANCE

- Surveillance should be considered in patients staged I-III who are candidate for salvage surgery.
- Follow up recommendations should be provided to the patients and their primary care physicians.
- CEA testing every 3-6 months for the first 3 years then every 6 months until 5 years.
- Progressive CEA rises warrants a work-up for recurrent /metastatic disease.
- Consider periodic clinical assessment.
- CT scan of the thorax, abdomen, and pelvis (for rectal cancer) every 12-18 months in first three years.
- More frequent imaging study may be considered in patients who had stage IV disease and underwent complete resection of metastatic lesions (i.e. every 3-6 months in the first two years and every 6-12 months in the subsequent three years).

- Flexible procto-sigmoidoscopy every 6 months for 5 years for rectal cancer patients not treated with pelvic radiation
- Routine CBC, LFT, fecal occult blood tests, or other imaging studies are not recommended unless clinically indicated

CHEMOTHERAPY REGIMENS

Adjuvant Therapy

5-FU + LV (biweekly infusional regimen)

Leucovorin 400 mg/m² iv day1

5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv over 46 hrs

Every 2 weeks for 12 cycles

5-FU + LV (Roswell park regimen)

Leucovorin 500 mg/m² iv over 2 hours

5-FU 500 mg/m² iv bolus 1 h after the start of Leucovorin

Once a week for 6 weeks every 8 weeks for 3 to 4 cycles

5-FU + LV (Mayo clinic regimen)

Leucovorin 20-25 mg/m²/d iv bolus day 1 to5

5-FU 370-425 mg/m²/d iv bolus day 1 to 5

Every 4 weeks for 6 cycles

Capecitabine

Capecitabine 1250 mg/m² po bid x 14 days

Every 3 weeks for 8 cycles.

Modified FOLFOX6

Leucovorin 400 mg/m² iv day1

5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv over 46 hrs

Oxaliplatin 85 mg/m² iv day1

Every 2 weeks for 12 cycles.

CapeOX

Capecitabine 1000 mg/m² po bid x 14 days

Oxaliplatin 130 mg/m² iv over 2 hrs day1

Every 3 weeks for 8 cycles.

Advanced Disease

FOLFOXIRI +/- Bevacizumab

5-FU + Irinotecan + Oxaliplatin

Irinotecan 165mg/m² IV Day 1

Oxaliplatin 85mg/m² IV Day1

Leucovorin 200mg/m² IV Day1

5-FU 3,200mg/m² continuous IV infusion

Bevacizumab 5mg/kg IV Day 1 (if added to Chemo backbone)

Q 2 weeks protocol

5-FU + LV (biweekly infusional regimen)

Leucovorin 400 mg/m² iv day1

5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv over 46 hrs

Every 2 weeks.

5-FU + LV (Roswell park regimen)

Leucovorin 500 mg/m² iv over 2 hours

5-FU 500 mg/m² iv bolus 1 h after the start of Leucovorin

Once a week for 6 weeks every 8 weeks.

5-FU + LV (Mayo clinic regimen)

Leucovorin 20-25 mg/m²/d iv bolus day 1 to5

5-FU 370-425 mg/m²/d iv bolus day 1 to 5

Every 4 weeks.

FOLFIRI

Leucovorin 400 mg/m² iv day1

5-FU 400 mg/m² iv bolus day1, and then 2400 mg/m² iv over 46 hrs

Irinotecan 180 mg/m² iv over 90 min day1

Every 2 weeks.

Modified FOLFOX6

Leucovorin 400 mg/m² iv day1

5-FU 400 mg/m² iv bolus day1 followed by 2400 mg/m² iv over 46 hrs

Oxaliplatin 85 mg/m² iv day1

Every 2 weeks.

CapeOX

Capecitabine 1000 mg/m² po bid x 14 days

Oxaliplatin 130 mg/m² iv over 2 hrs day1

Every 3 weeks.

Capecitabine

Capecitabine 1000 mg/m² po bid x 14 days

Every 3 weeks.

Cetuximab + Irinotecan

Cetuximab 500 mg/m² iv over 1 to 2 hour every 2 weeks
Irinotecan 180 mg/m² iv every 2 weeks x 4 wks
Every 6 weeks.

Panitumumab

Panitumumab 6 mg/kg iv over 60 min day1
Every 2 weeks.

Concurrent Chemoradiotherapy Regimens**5-FU + RT**

5-FU 225 mg/m²/day civi
Concurrent radiotherapy

Capecitabine + RT

Capecitabine 825 mg/m² po bid x 5 to 7 days/week
Concurrent radiotherapy

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Additional Resources

1. Cancer Statistics: <http://www.cancer.ca/Canada>
2. <http://www.cancer.gov/cancertopics/types/colon-and-rectal>
3. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
4. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/default.htm?wb_c_purpose=Basic&WBCMODE=PresentationUnpublished%23cultural
5. <http://www.cancercare.on.ca/cms/one.aspx?objectId=80771&contextId=1377>
6. <http://guidance.nice.org.uk>
7. <https://doi.org/10.1093/annonc/mdx738> (Pan-Asian adapted ESMO consensus guidelines. *Annals of Oncology*, Volume 29, Issue 1, 1 January 2018, Pages 44–70,
8. Western Canadian Gastrointestinal Cancer Consensus Conference 2014, 2017 and 2018.