Provincial Colorectal Cancer Treatment Guidelines

As per consensus at the Provincial Colorectal Cancer Meeting, June 17, 2011

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. 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 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
3) Colonoscopy
4) Biopsy & pathology
5) MSI testing in stage 2 colon cancer patients
6) K-RAS testing if anti-EGFR monoclonal antibodies therapy is a consideration
7) CT chest/abdomen/pelvis
8) EUS and endorectal coil or pelvic MRI for staging in rectal cancer
9) PET/CT or MRI abdomen (Can be considered 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.

1. LOCALIZED COLON CANCER (Stage I-III)

Surgery

- Complete resection of the tumor with clear margins (R0) and removal of local lymph nodes.
- A minimum of 12 lymph nodes examination is preferred to determine N stage.

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 till more data is available. It can be considered in selected patients younger than 70 yrs of age with multiple high risk factors.

- Poor prognostic features:
  - T4
  - 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+): 6 months of FOLFOX or CapeOx.

  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 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 regarding role of radiation. Effort should be made by surgeon to mark areas of suspicious margin status.

2. **LOCALIZED RECTAL CANCER (Stage I-III)**

**Surgery**

- Total Mesorectal Excision with removal of local lymph nodes.

- A minimum of 12 lymph nodes examination is preferred to determine N stage in patients.

**Chemoradiation**

- Stage I (T1N0 or T2N0): Surgery alone and no adjuvant therapy recommended.

- Selected, T2N0, low rectal tumors may be considered for neo-adjuvant chemotherapy and radiation 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 6-8 weeks followed by adjuvant chemotherapy with 5-FU or Capecitabine or FOLFOX (total duration of perioperative therapy is 6 months).
  - In patients, ≥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) could be considered, followed by surgery in 7-10 days.
• If surgery is performed upfront: ≥pT3 and/or node positive disease. Adjuvant chemo radiotherapy with 5-FU or Capecitabine and radiation followed adjuvant chemotherapy with 5-FU or Capecitabine or FOLFOX (total duration of therapy is 6 months).

• 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.

3. LOCALLY ADVANCED UNRESECTABLE COLORECTAL CANCER

- Combination chemotherapy + Bevacizumab or Cetuximab/Panitumumab in KRAS wild type tumors (if applicable). Both targeted agents have shown higher response when combined with combination chemotherapy.

- Radical, concurrent chemotherapy with 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.

4. 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 (total duration of treatment = 6 months) may be considered in selected cases.

- Consider incorporating radiation therapy to the primary tumor site (rectal cancer).

5. POTENTIALLY RESECTABLE METASTATIC COLORECTAL CANCER (Stage IV)

- For Lung or Liver or selected peritoneal metastasis

- FOLFOX or FOLFIRI ± Bevacizumab or Cetuximab/Panitumumab in KRAS wild type tumors in selected cases.

- Reassessment for conversion to surgical resection every 2 months.
Consider incorporating radiation therapy to the primary tumor site (rectal cancer).

Hold off on Bevacizumab or Cetuximab/Panitumumab if R0 resection.

6. UNRESECTABLE METASTATIC COLORECTAL CANCER (Stage IV)

- 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
- FOLFIRI (preferred) or FOLFOX ± Bevacizumab. Alternatively FOLFIRI in combination with Cetuximab can be considered in KRAS wild type tumor.
- In selected patients after 3 to 6 months of induction therapy, consider maintenance therapy with a 5-FU ± Bevacizumab until progression. If progression of disease while on maintenance therapy re-introduce FOLFIRI ± 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 with a 2nd line fluoropyrimidine-based chemotherapy regimen or alternatively Aflibercept in combination with 2nd line chemotherapy or in KRAS wild tumor 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. If 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
- K-RAS wild type tumors: If previously not received anti-EGFR monoclonal antibodies consider Cetuximab or Panitumumab as single agent or Irinotecan in combination with Cetuximab
- K-RAS mutated tumor: Regorafenib has shown modest benefit and can be considered in patients with good performance status.

4th line therapy
• K-RAS wild type tumors: K-RAS mutated tumor: Regorafenib has shown modest benefit and can be considered in patients with good performance status.

7. Surveillance

- In patients treated with curative intent, history and physical examination every 3-6 months for first three years and then every 6-12 months for the next two years and annually thereafter.

- CEA testing every three to six months for first three years then every 6 to 12 months for total of five years for T2 or greater lesions. Progressive CEA rises warrant a work-up for recurrent disease.

- Consider CT scan of the thorax, abdomen, and pelvis (for rectal cancer) annually for three years in high risk patients who might be candidates for salvage surgery or palliative chemotherapy. 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). Most of the colon cancer relapses are within 3 years therefore follow-up with CT can be done for three years. Rectal cancer relapses can be late and therefore require long term follow-up probably up to 7 to 10 years.

- Repeat colonoscopy one year post surgery (and annually until free of polyps), then every 3-5 years thereafter. If no full length preoperative colonoscopy was undertaken, schedule for 3-6 months post initial surgery to exclude synchronous malignancy or polyps.

- 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 (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 to 5
5-FU 370-425 mg/m2/d iv bolus day 1 to 5
Every 4 weeks for 6 cycles

5-FU + LV (Simplified 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

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.

Chemotherapy Regimens (Advanced Disease)

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.

5-FU + LV (Simplified 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.

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.

Bevacizumab
Bevacizumab 5 mg/kg iv day1
Every 2 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 references/resources