



Provincial Esophageal Cancer and Gastro-esophageal Junction Cancer Treatment Guidelines

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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. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. 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 the Agency.

Recommendations for drug treatment presented in the Agency's guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca 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.

- Esophageal cancer generally portends a poor prognosis. Approximately 50-60% of patients will present with advanced disease not amenable to treatment with curative intent. A small minority will present with early stage disease and outcomes with surgical resection are good. However, by the time patients present with dysphagia the tumour has penetrated the esophageal wall and the likelihood of lymph node metastases is very high. These patients are most commonly evaluated for potential multi-modality therapy involving chemoradiation and surgery. Since the mid 1970s, the incidence of esophageal squamous cell carcinoma in North America has been declining steadily, Adenocarcinoma has surpassed SCC as the dominant histology in the early 1990s.
- Given the complex nature of esophageal cancer management, all patients considered for curative intent treatment should be evaluated in a multi-disciplinary manner. Optimally this team should comprise of radiologists, nuclear medicine specialist, gastroenterologists, pathologists, medical and radiation oncologists, and surgeons.
- Staging is based on the AJCC TNM system. T stage is defined as depth of invasion into the esophageal wall and whether or not it invades surrounding structures. N stage refers to the number of lymph nodes involved and M indicates metastatic disease. Clinical staging involves a combination of clinical and radiological investigations briefly outlined below. The purpose of which is to determine which patients are potentially curable (Stage I-III) and those that are not (Stage IV).
- Given lack of data of impact of histology on treatment result, with few exception both squamous and adenocarcinoma are treated similarly. However the additional benefit of surgery after chemotherapy and radiation is less clear in squamous cell cancers and definite chemoradiation is an acceptable option.

A. ASSESSMENT AND INVESTIGATIONS

- History and physical examination
- CT scan of chest and abdomen
- Endoscopic examination (indicating the location of the tumour from the incisors, length of the tumour, nature of tumour i.e. polypoid, exophytic, ulcerated, extension into the stomach, percentage of circumference involved)
- Biopsy (Her2/neu overexpression in patients with adenocarcinoma of gastro-esophageal junction with distant metastasis.)
- Nutritional evaluation: Consider placement of a gastric feeding tube for patients deemed to be candidates for trimodality therapy.

For multimodality therapy further studies may be required for T and N staging

- Endoscopic ultrasound examination (EUS): Endoscopic ultrasound (EUS) is useful in early lesions in order to assess tumour depth and lymph node status those patients amenable to upfront surgery or candidates for tri-modality treatment (T3N0, T1-4a and any locoregional N). EUS can assess T stage; however, role in stenotic carcinomas is questionable as clinically they are T3 cancer. Furthermore, in the stenotic cancers, EUS requires dilation of the tumour which risks perforating the esophagus.
- MRI for T staging and invasion of adjacent structures
- PET/CT scan is strongly recommended for patients undergoing curative treatment.
- Diagnostic laparoscopy for T3N+ GE adenocarcinoma for occult disease
- Bronchoscopy for lesions at or above the carina to evaluate for airway involvement (T4b).

B. TREATMENT**B1. Stage 0 Tis (Barrett's esophagus with High Grade Dysplasia)**

- Radiofrequency ablation (RFA) with or without endomucosal resection (EMR). Esophagectomy if invasive carcinoma detected in EMR specimen.
- Upfront esophagectomy is an alternate option.

B2. Stage 1 T1, N0, M0 (GOOD PERFORMANCE STATUS)

- Surgery alone is the treatment of choice
- All suspected Tis, and T1 lesions should have submucosal resections to adequately determine depth of invasion and to determine if ablative therapy is an option.
- For T1a endomucosal resection + ablation or esophagectomy
- For T1b esophagectomy because of the high risk of lymph node metastases
- Definite chemoradiation therapy can be considered in medically unfit patients for surgery or if patient decline surgery
- Radical radiation alone to a dose of 54-60Gy in 1.8 to 2Gy per fraction may be considered in selected patients refusing or medically unfit for surgery and chemotherapy

B3. Cervical Esophageal Carcinoma

- Squamous cell carcinoma of cervical esophagus are generally recommended to undergo definite radiation therapy and chemotherapy.
- Salvage esophagectomy can be completed for residual/recurrent disease.
- In patients with squamous cell carcinoma of cervical esophagus (Cisplatin /5FU ×2 cycles concurrent with radiation followed by 2 more cycles of chemotherapy. Radiation doses range from 45 -59.4 Gy /25- 33fractions)
- Higher radiation dose to be considered for squamous cell cancer of cervical esophagus.

B4. Stage 2 & 3 (Selected T2)/ T3/T4, N0/N+, M0 (GOOD PERFORMANCE STATUS)

Multimodality therapy (pre-operative chemoradiotherapy followed by surgery) is strongly recommended in patients with \geq stage II esophageal cancers. Following induction treatment, clinical and radiographic re-evaluation prior to surgical resection is strongly recommended. Post-induction evaluation may include CT chest/abdomen/pelvis, PET/CT, EUS or diagnostic laparoscopy based on the clinical situation.

- Weekly carboplatin/paclitaxel and RT (doses of 41.4 Gy in 23 fractions or 45 - 50.4 Gy in 25 - 28 fractions) for patients with T1N1 or T2-3N0-1 disease as per the CROSS protocol followed by surgery in 4 - 6 weeks is the preferred regimen.
- Cisplatin/5FU and external RT doses of 45 - 50.4 Gy in 25 - 28 fractions is alternate to the CROSS protocol.
- For adenocarcinoma of the gastro-esophageal junction and distal esophagus pre-operative chemotherapy with 4 cycles of FLOT regimen (Docetaxel, 5FU, Leucovorin and Oxaliplatin) before surgery and 4 cycles after surgery - based on FLOT4-AIO trial presented in ASCO 2017 can be considered, if chemoradiation is not a consideration. For patients not fit to be considered for FLOT regimen, ECF/ECX/EOX/EOF for 3 cycles followed by surgery followed by 3 cycles of chemotherapy as per MAGIC protocol is an option.
- In selected patients with esophageal cancer 2 cycles chemotherapy with Cisplatin/5FU followed by surgery in 4 - 6 weeks' time as per JCOG-9907 protocol can be considered.
- Definite chemoradiation therapy can be considered in medically unfit patients for surgery or if patient decline surgery or in patients with squamous cell carcinoma of cervical esophagus (Cisplatin /5FU \times 2 cycles concurrent with radiation followed by 2 more cycles of chemotherapy or 6 cycle of modified FOLFOX - Oxaliplatin 85mg/m², Leucovorin 200mg/m², bolus 5FU 400mg/m², infusional 5FU 1600mg/m² - 2 weekly, 3 cycle with radiotherapy and 3 following - per PRODIGE5/ACCORD17 protocol). Radiation doses range from 45 - 50.4 Gy /25-28 fractions)
- Radical radiation alone to a dose of 54 - 60Gy in 1.8 to 2Gy per fraction may be considered in selected patients refusing or medically unfit for surgery and chemotherapy

B5. T1-T4, N0/N+, M0 (POOR PERFORMANCE STATUS)

- Palliative radiotherapy (40Gy/ 16 fractions, 36Gy/12 fractions, 30Gy/10 fractions, 20Gy/5 fractions, 8Gy/1 fraction).
- Palliative chemotherapy.
- Best supportive care.
- Palliative stenting for relief of dysphagia.
- Intra-luminal brachytherapy may be considered in selected patients.

B6. ADJUVANT THERAPY AFTER SURGERY (THORACIC, MID AND DISTAL ESOPHAGUS)

- Currently no randomized clinical trial is available to answer the question if adjuvant therapy offers any benefit in this group of patients. In selected group of patients (node +ve or T2/T3 with high risk features such as high grade, LVI, perineural invasion and age of less than 50) this option could be considered after discussion with the multidisciplinary tumour group.

B7. ADJUVANT THERAPY AFTER SURGERY (GASTRO-ESOPHAGEAL JUNCTION ADENOCARCINOMA)

- pT2 - T3 - T4, or node positive disease or R1 resection: Adjuvant chemoradiation with 5-fluorouracil is recommended in patients with good performance status who did not receive pre-operative therapy as per the Inter-Group protocol.

B8. METASTATIC DISEASE (M+)

Palliative chemotherapy (Combination of chemotherapy can be considered in patients with good performance status).

- First line combination therapy –Cisplatin/5FU and the three drug combinations with ECF, ECX, EOX, or FOLFOX are acceptable regimens. DCF has been associated with substantial grade 3-4 toxicities and is not routinely recommended. Response rates and survival are modestly better with the three drug combinations.
- Cisplatin /5FU/Herceptin can be used in Her2 positive adenocarcinoma of GE junction.
- Second line – There is no standard chemo regimen. Taxanes (docetaxel or paclitaxel) or Irinotecan alone or in combination with 5FU (FOLFIRI) can be considered in patients with good performance status.
- Palliative radiotherapy (40Gy/ 16 fractions, 36Gy/12 fractions, 30Gy/10 fractions, 20Gy/5 fractions, 8Gy/1 fraction).
- Best supportive care.
- Palliative stenting for relief of dysphagia.
- Intra-luminal brachytherapy may be considered in selected patients.

C. SYSTEMIC THERAPY

C1. SINGLE AGENT CHEMOTHERAPY

- Doxorubicin, cisplatin, 5-fluorouracil (5-FU) and etoposide are associated with modest response rates of short duration (usually less than six months). Carboplatin has not been as widely studied as cisplatin, but it appears to be less active. Newer generation single agent paclitaxel, docetaxel or Irinotecan produce response rates in 15-25% range.

C2. COMBINATION CHEMOTHERAPY

- Combination chemotherapy leads to higher response rates and modest improvement in survival. The combination of cisplatin plus 5-FU is one the best studied and the most commonly used regimens in due to its proven activity and well-established toxicity profile. Response rates can be seen in 25 percent of patients and toxicity may be improved if the cisplatin is split over 3-5 days.
- In a randomized phase III study, 4 regimens, ECF (Epirubicin /Cisplatin/ infusional 5FU), EOF (Epirubicin /Oxaliplatin /infusional 5FU), ECX (Epirubicin /Cisplatin /Capecitabine), and EOX (Epirubicin /Oxaliplatin /Capecitabine) were assessed in patients with advanced esophageal and gastric cancers. There were no significant differences among the groups in terms of objective response rate (41, 42, 46, and 48 percent with ECF, EOF, ECX, and EOX, respectively), progression-free survival or toxicity. Median survival in patients treated with EOX was modestly longer when compared to ECF (median 11.2 versus 9.9 months).
- A meta-analysis concluded that, compared to 5-FU combinations, Capecitabine combinations were associated with higher response rates (odds ratio 1.38, 95% CI 1.10-1.73) and better overall survival (hazard ratio for death 0.87, 95% CI 0.77-0.98). FOLFOX has also been compared to ECF with comparable results.
- Docetaxel or paclitaxel combinations with cisplatin, carboplatin, 5-FU, or Capecitabine are active in advanced gastric and esophageal cancer, however 3 drugs combination appears to be more toxic. Irinotecan based FOLFIRI also appears to be an active regimen in advanced gastric and esophageal adenocarcinoma.

C3. BIOLOGICAL THERAPY

Her-2 positive Gastro-esophageal Junction cancers

- Approximately 22 percent of gastric and GE junction tumours overexpress the type II EGFR (HER2). The benefit of Trastuzumab in advanced HER2-positive adenocarcinoma of the stomach or GE junction was addressed in the phase III ToGA trial, which compared standard chemotherapy (six courses of cisplatin plus either infusional 5-FU or Capecitabine) with and without Trastuzumab every three weeks until disease progression
- Response rate was significantly higher with Trastuzumab (47 versus 35 percent). Median overall survival (the primary endpoint) was significantly better with Trastuzumab (13.8 versus 11.1 months). There are no data addressing the benefit of continuing Trastuzumab with the second-line regimen.

C4. Second line therapy

- Second-line chemotherapy regimens after failure of the first-line regimen have generally shown lower response rates and greater toxicity. There is no standard approach for second-line therapy.
- For patients with good performance status, utilization of other active agents not used in the first-line regimen is reasonable, either in combination or as serial single agents.
- For GEJ tumours, Ramucirumab plus Paclitaxel or Ramucirumab could be considered as if funding is access is available – per RAINBOW trial protocol.
- For selective group of patients with known MSI status, immunotherapy could be a consideration if access is available.

D. SURGICAL APPROACHES

- Most adenocarcinomas of the esophagus develop within the lower thoracic esophagus or gastro-esophageal junction (GEJ). The anatomical landmarks of which are the inferior edge of the inferior pulmonary vein to the GEJ. This extends from approximately 32 cms from the incisors to 40cms. A transthoracic (Ivor-Lewis), trans hiatal, thoracoabdominal or three-field esophagectomy (McKeown) are acceptable approaches to tumours of the lower esophagus with a tubularized stomach being the conduit of choice. The degree of lymphadenectomy is debated, however, it is recommended that at a minimum, lymph node sampling should be undertaken. This recommendation is based on studies showing improved survival in patients with more lymph nodes removed at surgery. Pyloromyotomy or pyloroplasty may consider to prevent gastric outlet obstruction in the post-operative period. A feeding jejunostomy is also considered based on the patients preoperative nutritional status.
- Anatomically squamous cell carcinomas more often present within the upper/middle thoracic and cervical esophagus. Treatment of squamous cell carcinoma mirrors that of adenocarcinoma because studies do not differentiate between the two histologies. There are a few exceptions.
- Evaluation of the airway is necessary for all lesions at or above the carina to assess for airway involvement. Upper/middle esophageal squamous cell carcinomas the location of these tumours, most are approached via a three-field approach (McKeown). Cervical lesions require the involvement of ENT as well as the aforementioned multidisciplinary team. A pharyngolaryngoesophagectomy with gastric conduit reconstruction is performed in patients who are treated with definitive chemoradiation and have residual disease and involved bilateral radical neck dissection plus removal of parts of pharynx, larynx, thyroid, and part of proximal esophagus.

E. FOLLOW-UP AFTER CURATIVE THERAPY

Follow-up investigations should be tailored based on disease stage, adjuvant treatment provided, performance status, and clinical signs and symptoms. There is lack of level 1 evidence with respect to optimal follow up of patients with esophageal and GE junction cancer who are treated with curative intention.

- In patients treated with curative intent: history and physical examination every 3–6 months for the first 3 years then every 6–12 months for the next 2 years and annually thereafter.
- Routine imaging studies such as thoracoabdominal CT scan, abdominal ultrasound and chest x-ray are not recommended and can be performed as clinically indicated.
- Endoscopic examination as clinically indicated.
- Laboratory testing including CBC, serum chemistry, LFT, and CEA only as clinically indicated.
- Nutritional counseling should be performed for all patients.
- All patients should be educated to seek medical attention if they developed abnormal symptoms.

F. APPENDIX (CHEMOTHERAPY REGIMENS)

F1. Preop Chemotherapy alone (Esophagus)

1. Cisplatin 80mg/m² Day1, 5FU 1000 mg/m² Day1-4 continuous infusion (q 21 Days × 2 cycles).

F2. Peri Operative Chemotherapy alone (Lower Esophageal/GE junction adenocarcinoma)

1. Epirubicin 50mg/m², Cisplatin 60mg/m², 5FU 200 mg/m² CVI (q 21 Days × 3 cycles Pre/Post op).
2. Epirubicin 50mg/m², Cisplatin 60mg/m², Capecitabine 625mg/m² continuous (q 21 Days × 3 cycles Pre/Post op).

F3. Preop Chemo Radiation

1. Carboplatin AUC2, Taxol 50mg/m² (weekly for 5 weeks with RT)
2. Cisplatin 75mg/m² D1 or 25mg/m² D1-3, 5FU 1000 mg/m² D1-4 (2 cycles week 1+5 with RT)

F4. Definitive Chemoradiotherapy (Esophagus)

1. Cisplatin 75mg/m² D1 or 25mg/m² D1-3, 5FU 1000 mg/m² D1-4 (2 cycles Week 1+5 with RT, 2 more cycles 3 weekly to start 3 weeks after radiation). Capecitabine can be substituted for 5FU

F5. Adjuvant ChemoRT for GE junction Adenocarcinoma

Chemotherapy, 5FU 425mg/m² IV Day 1-5, Folinic Acid 20mg/m² IV Day 1-5 → RT to start on Day1 of week 5. (RT dose is 45GY in 25 Fractions)

Week 1 of ChemoRT: 5FU 400mg/m² IV Day 1-4, Folinic Acid 20mg/m² IV Day 1-4.

Week 5 of ChemoRT: 5FU 400mg/m² IV Day 1-3, Folinic Acid 20mg/m² IV Day 1-3

4 weeks following RT: Further 2 cycles of every 28 days

5FU 425mg/m² IV Day 1-5, Folinic Acid 20mg/m² IV Day 1-5.

Alternatively continuous infusion 5FU 200 to 250mg/m²/day during the whole duration of radiation therapy can be considered.

F6. Palliative chemotherapy

1. Epirubicin 50mg/m², Cisplatin 60mg/m², 5FU 200 mg/m² CVI (q21 Days, up to 6 cycles).
2. Epirubicin 50mg/m², Cisplatin 60mg/m², Capecitabine 625mg/m² continuous (q21 Days, up to 6 cycles).
3. Cisplatin 75mg/m² D1 or 25mg/m² D1-3, 5FU 1000 mg/m² D1-4 (q21 Days, up to 6 cycles)
4. Consider listing FOLFOX/FOLFIRI as options
5. Cisplatin 80 mg/m² D1, 5FU 800mg/m² D1-5 CVI, Herceptin 8mg/kg LD after 6 cycles if no progression, Herceptin 6mg/kg MD (q21 Days, up to 6 cycles. Herceptin can be continued after 6 cycles if no progression). Capecitabine can be substituted for 5FU. For patients with poor performance status or reduced Creatinine clearance, consider Carboplatin instead of Cisplatin.

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Additional resources

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www.cancer.gov

www.bccancer.bc.ca

www.cancercare.on.ca

www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines

www.uptodate.com

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