ESOPHAGEAL CANCER

Effective Date: March 2016

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gastrointestinal 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.
BACKGROUND

There are two common distinct histologies of esophageal cancer. Chronic gastroesophageal reflux predisposes to Barrett’s metaplasia and the development of adenocarcinoma. Typically, it develops within the distal esophagus; it is now more prevalent than the other histology, squamous cell carcinoma. The recognized risk factors for squamous cell carcinoma include tobacco and alcohol exposure.

A multidisciplinary team (composed of radiologists, gastroenterologists, pathologist, thoracic and general surgeons, both radiation and medical oncologists, nurses, and dieticians) is required to review the results of the diagnostic work-up and to establish the optimal care for a patient with esophageal cancer.

This guideline was developed to outline the management recommendations for patients with esophageal cancer (both squamous cell carcinoma and adenocarcinoma).

GUIDELINE QUESTIONS

- What are the recommendations for the diagnostic workup of adult patients with esophageal cancer?
- What are the recommendations for treatment of adult patients with potentially curable esophageal cancer?
- What are the recommendations for management of adult patients with incurable esophageal cancer?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists, gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist 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 March 2010. This guideline was revised in June 2011, October 2013 and March 2016.

SEARCH STRATEGY

This guideline was developed to promote evidence-based practice in Alberta. 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. It takes into consideration related information presented at local, national, and international meetings as well as the Alberta Provincial Gastrointestinal Tumour Team’s interpretation of the data. The 2016 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2015 Annual Gastrointestinal Tumour Team Meeting.
TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with esophageal cancer, including both squamous cell and adenocarcinoma. Different principles may apply to pediatric patients.

RECOMMENDATIONS AND DISCUSSION

Recommended Diagnostic Work-Up

- Esophagogastroduodenoscopy with biopsy establishes the tumour’s location (distance from incisors) and histology.
- An augmented CT scan of the thorax and abdomen also helps to establish the tumour’s location, depth of penetration into the esophageal wall, invasion into adjacent structures, and involvement of regional and non-regional lymph nodes. Metastatic disease confers an incurable situation for which only palliative maneuvers would be appropriate.
- Blood work identifies any end-organ dysfunction that may preclude the safe administration of chemotherapy.

Optional Investigations:

- In the absence of metastatic disease (based upon the above investigations), the following tests may be of additional value:
  - Endoscopic ultrasound (establishes the depth of penetration into the esophageal wall, invasion into adjacent structures, and involvement of regional and non-regional lymph nodes);
  - Pulmonary function testing (required prior to surgical resection and may be necessary prior to chemoradiotherapy); and/or
  - F-fluorodeoxy-D-glucose (FDG) PET scan can complement an augmented CT scan and help to identify radiologically-occult metastatic disease. In certain cases, FDG-PET can provide an assessment of response.
Table 1. AJCC Staging System for Esophageal Cancer, Seventh Edition.\textsuperscript{13}

<table>
<thead>
<tr>
<th>Stage Information</th>
</tr>
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</table>

### Definition

**Depth of Tumor Penetration (T Stage):**
- \( T_0 \): Carcinoma in situ or high-grade dysplasia
- \( T_1 \): Invasion into lamina propria or submucosa
- \( T_2 \): Invasion into muscularis propria
- \( T_3 \): Invasion into adventitia
- \( T_{4a} \): Invasion into resectable adjacent structures (e.g., pleura, pericardium, diaphragm)
- \( T_{4b} \): Invasion into unresectable adjacent structures (e.g., aorta, vertebral body, trachea)

### Histologic Grade (G Stage):
- \( G_1 \): Well differentiated
- \( G_2 \): Moderately differentiated
- \( G_3 \): Poorly differentiated
- \( G_4 \): Undifferentiated

### Regional Lymph Node Involvement (N Stage):
- \( N_0 \): No regional lymph node involvement
- \( N_1 \): Involvement of one or two regional lymph nodes
- \( N_2 \): Involvement of three to six regional lymph nodes
- \( N_3 \): Involvement of seven or more regional lymph nodes

*Regional* refers to any peri-esophageal lymph node (from cervical to celiac regions)

### Histology

<table>
<thead>
<tr>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td><strong>L</strong></td>
</tr>
<tr>
<td>Stage 0</td>
<td>Any</td>
</tr>
<tr>
<td>Stage Ia</td>
<td>Any</td>
</tr>
<tr>
<td>Stage Ib</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIa</td>
<td>U or M</td>
</tr>
<tr>
<td>Stage IIb</td>
<td>U or M</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIc</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any</td>
</tr>
</tbody>
</table>

**Risk-Adjusted Survival (%)**

![Risk-Adjusted Survival Graph](image-url)
Goals of Therapy

To render the patient free of disease, to delay or prevent recurrence, to relieve symptoms (e.g.: dysphagia), and to improve or prolong survival, if possible.

Recommendations:\textsuperscript{14}

- Complete a work-up (as described above) and review the patient’s case with the multidisciplinary team. Early referral to a surgeon trained in esophageal surgery is important to assess for resectability.
- Assess the degree of dysphagia and consult with a dietician to optimize the patient’s nutritional status. Consider placement of a nasogastic (NG) feeding tube. If the NG feeding tube insertion is technically difficult, placement should be performed radiographically. In a curative situation, avoid placement of an endoluminal stent as it increases the complication and mortality rate with radical chemoradiotherapy.\textsuperscript{15}
- If an esophagectomy with conduit reconstruction (“gastric pull-up” procedure) is anticipated for a tumour of the gastroesophageal junction, please refer the patient for consideration of peri-operative chemotherapy.
- Consider treatment on a clinical trial, if available.

Table 2. Curative Therapy Recommendations for Patients with Esophageal Cancer.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recommendations</th>
<th>Description</th>
<th>Chance of Lymph Node Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>T\textsubscript{1a}N\textsubscript{0} or T\textsubscript{1b}N\textsubscript{0} Disease</td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Presence in the epithelial layer of the mucosa</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Invasion into lamina propria mucosal</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Invasion into (but not through) muscularis mucosae</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Invasion into superficial third of submucosa</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Invasion into middle third of submucosa</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td><strong>Endoscopic Therapy:</strong></td>
<td>Invasion into deepest third of submucosa</td>
<td>49%</td>
</tr>
</tbody>
</table>

\textbf{Modified Dysphagia Score}\textsuperscript{16}

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ability to eat normal diet</td>
</tr>
<tr>
<td>1</td>
<td>Ability to eat some solid food</td>
</tr>
<tr>
<td>2</td>
<td>Ability to eat semisolids only</td>
</tr>
<tr>
<td>3</td>
<td>Ability to swallow liquids only</td>
</tr>
<tr>
<td>4</td>
<td>Complete dysphagia</td>
</tr>
</tbody>
</table>
Primary (‘Definitive’) Chemoradiotherapy:
- Consider for patients in whom endoscopic mucosal resection and/or photodynamic therapy are contraindicated (e.g.: patients with varices secondary to liver disease) or in whom it is not possible to resect the disease due to medical or technical issues. The two treatment options are:
  - Deliver 5,000 cGy in twenty-five fractions over five weeks plus Cisplatin 75 mg/m² IV over one hour and 5-Fluorouracil 4,000 mg/m² IV over ninety-six hours on weeks one, five, eight, and eleven. This protocol offers an eight-year overall survival rate of 26% (compared to 0% for radiotherapy alone).²¹
    Note: 82% of the patients enrolled had squamous cell carcinoma of the esophagus.
  - Deliver 5,000 cGy in twenty-five fractions over five weeks plus Oxaliplatin 85 mg/m² IV and Leucovorin 200 mg/m² IV followed by 5-Fluorouracil 400 mg/m² IV bolus followed by 5-Fluorouracil 800 mg/m²/day over days one and two on weeks one, three, five, seven, and eleven. When compared to the above regimen, this regimen is associated with less mucositis, alopecia, and renal toxicity plus numerically fewer toxic and sudden deaths but without a difference in overall survival, progression-free survival, and pCR rate.²² Director’s Privileges are required to pursue this option.
- These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port.

Alternative Radiotherapy Alone:
- Consider for patients in whom endoscopic mucosal resection and/or photodynamic therapy are contraindicated (e.g.: patients with varices secondary to liver disease), in whom it is not possible to resect disease due to medical or technical issues, or in whom chemotherapy is deemed unsafe.

Pre-Operative Chemoradiotherapy followed by Esophagectomy (if possible):
- In a meta-analysis of 1,209 patients in ten randomized trials, pre-operative chemoradiotherapy (“tri-modality therapy”) improves the survival of patients with potentially resectable esophageal cancer irrespective of histology.²³ For adenocarcinoma, pre-operative chemoradiotherapy offers a 25% reduction in the risk of death (HR 0.75, CI95% 0.59-0.95, \( p = 0.02 \)). For squamous cell carcinoma, pre-operative chemoradiotherapy offers a 16% reduction in the risk of death (HR 0.84, CI95% 0.71-0.99, \( p = 0.04 \)).
- Deliver 4,140 cGy in twenty-three fractions over five weeks plus Paclitaxel 50 mg/m² IV and Carboplatin AUC 2 IV on days 1, 8, 15, 22, and 29.²⁴ This protocol improves the R₀ resection rate (92% versus 69%) and overall survival (HR 0.657, CI95% 0.495-0.871, \( p = 0.003 \)) when compared to surgery alone. It prolongs median survival from 24.0 months to 49.4 months and increases the one-, two-, three-, and five-year survival rates from 70% to 82%, 50% to 67%, 44% to 58%, and 34% to 47% respectively. It offers a pCR rate of 23%. 75% of the patients enrolled had adenocarcinoma. About 25% of patients had disease at the esophagogastric junction.
  Note: Post-operative mortality is reduced and no benefit in progression-free survival, overall survival, or R₀ resection rate is achieved from the addition of two cycles of Cisplatin 75 mg/m² IV on days one and two and 5-Fluorouracil 3,200 mg/m² IV over ninety-six hours to 4,500 cGy in twenty-five fractions.²⁵
- Aim to achieve an “R₀” resection (no gross or microscopic residual tumour).
- Post-operative morbidity and survival are significantly better when surgery is completed in an experienced centre.¹⁷
- There is no data to guide further treatment in the setting of residual disease after pre-operative chemoradiotherapy and surgery.
Alternative Recommendations

**Peri-Operative Chemotherapy:**
- When compared to surgery alone in patients with good performance status (ECOG ≤1) and T2–4N0–3M0 adenocarcinoma of the distal third of the esophagus, gastro-esophageal junction, or stomach, peri-operative chemotherapy improves the five-year progression-free (HR 0.66, CI95% 0.53-0.81, \( p < 0.001 \)) and overall survival (from 23.0% to 36.3%, HR 0.74, CI95% 0.59-0.93, \( p = 0.008 \)).
- **Pre-Operative Phase:** Three three-week cycles of Epirubicin 50 mg/m² and Cisplatin 60 mg/m² IV on day one plus a continuous intravenous infusion of 5-Fluourouracil 200 mg/m²/day over twenty-one days.
- **Operative Phase:** Perform surgical resection with oncologic principles.
- **Post-Operative Phase:** As described in the pre-operative phase (above).
- Similarly, six four-week peri-operative cycles of Cisplatin 100 mg/m² IV on day one plus 5-Fluourouracil 800 mg/m²/day over days one through five days improves the five-year disease-free survival (34% versus 19%, HR 0.65, CI95% 0.48-0.89, \( p = 0.003 \)), overall survival (38% versus 24%, HR 0.69, CI95% 0.50-0.95, \( p = 0.02 \)), and rate of curative resection (84% versus 73%, \( p = 0.04 \)).
- These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port.

**Primary ('Definitive') Chemoradiotherapy:**
- Consider for patients in whom it is not possible to resect disease due to medical or technical issues. The two treatment options are:
  - Deliver 5,000 cGy in twenty-five fractions over five weeks plus Cisplatin 75 mg/m² IV over one hour and 5-Fluorouracil 4,000 mg/m² IV over ninety-six hours on weeks one, five, eight, and eleven. This protocol offers an eight-year overall survival rate of 26% (compared to 0% for radiotherapy alone).
  - Deliver 5,000 cGy in twenty-five fractions over five weeks plus Oxaliplatin 85 mg/m² IV and Leucovorin 200 mg/m² IV followed by 5-Fluorouracil 400 mg/m² IV bolus followed by 5-Fluorouracil 800 mg/m²/day over days one and two on weeks one, three, five, seven, nine, and eleven. When compared to the above regimen, this regimen is associated with less mucositis, alopecia, and renal toxicity plus numerically fewer toxic and sudden deaths but without a difference in overall survival, progression-free survival, and pCR rate. Director’s Privileges are required to pursue this option.
- These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port.

Recommendations for Incurable Situations

Provide palliative maneuvers to maintain and/or improve quality of life:
1. Relieve pain, bleeding, and/or dysphagia with radiotherapy.
2. Consider placement of an endoluminal stent or photodynamic therapy to relieve dysphagia.
3. Consider palliative chemotherapy to control disease and prolong survival in patients with a satisfactory performance status (ECOG ≤ 2).

**Table 3. ECOG Performance Status Scale.**

<table>
<thead>
<tr>
<th>ECOG</th>
<th>Description of Performance Status</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>
• Capecitabine-based combination regimens (e.g.: ECX, EOX, CX) offer a superior response rate (45.6% versus 38.4%, OR 1.38, CI95% 1.10-1.73, p = 0.006) and overall survival (HR 0.87, CI95% 0.77-0.98, p = 0.02) when compared to 5-Fluorouracil-based combination chemotherapies (e.g.: ECF, EOF, CF).

• ECX offers a median survival of about ten months and a one-year survival of around 40%. It is administered in three-week cycles where Epirubicin (50 mg/m² IV over twenty minutes) and Cisplatin (60 mg/m² IV over one hour along with hydration) are administered on day one. Capecitabine (625 mg/m² PO Q12h) is administered for twenty-one consecutive days.

• If a patient is unable to tolerate oral medications but remains a candidate for palliative chemotherapy, consider ECF. It is administered in three-week cycles as for ECX but, instead of Capecitabine, 5-Fluorouracil (200 mg/m²/day) is administered as a continuous intravenous infusion through a central venous catheter (“CVC”) or a peripherally inserted central catheter (“PICC line”).

• In a separate analysis of the REAL-2 clinical trial, thromboembolic events occur in 11.4% of patients (9.4% are venous events and 2.0% are arterial events). They undermine overall survival (7.4 months versus 10.5 months, HR 0.80, CI95% 0.64-0.99, p = 0.043). When compared to Cisplatin, Oxaliplatin confers a lower risk for thromboembolic events. A meta-analysis confirmed that the use of Oxaliplatin reduced the risk of death (HR 0.88, CI95% 0.78-0.99, p = 0.04), progression (HR 0.88, CI95% 0.80-0.98, p = 0.02), and thromboembolism. Director’s Privileges are required to pursue this option.

• Second line chemotherapy with Docetaxel (75 mg/m² IV every three weeks) improves overall survival (5.2 months versus 3.6 months, HR 0.67, CI95% 0.49-0.92, p = 0.01) and pain scores when compared with best supportive care.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>CF</td>
<td>cisplatin + 5-fluorouracil</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVC</td>
<td>central venous catheter</td>
</tr>
<tr>
<td>CX</td>
<td>cisplatin + capecitabine</td>
</tr>
<tr>
<td>ECF</td>
<td>epirubicin + cisplatin + 5-fluorouracil</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>ECX</td>
<td>epirubicin + cisplatin + capecitabine</td>
</tr>
<tr>
<td>EMR</td>
<td>endoscopic mucosal resection</td>
</tr>
<tr>
<td>EOF</td>
<td>epirubicin + oxaliplatin + 5-fluorouracil</td>
</tr>
<tr>
<td>EOX</td>
<td>epirubicin + oxaliplatin + capecitabine</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>fluorodeoxy-D-glucose positron emission tomography</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>NG</td>
<td>nasogastric</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PICC</td>
<td>peripherally inserted central catheter</td>
</tr>
<tr>
<td>TNM</td>
<td>tumour-node-metastasis</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gastrointestinal Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gastrointestinal Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


   Level of Evidence: 1a

   Level of Evidence: 1b

   Level of Evidence: 1b

   Level of Evidence: 1b

   Level of Evidence: 1b

   Level of Evidence: 2b

   Level of Evidence: 1a

   Level of Evidence: 2b

   Level of Evidence: 1a

   Level of Evidence: 1b

   Level of Evidence: 1b

   Level of Evidence: 1b

   Level of Evidence: 1a

   Level of Evidence: 1b


<table>
<thead>
<tr>
<th>Level</th>
<th>Description of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews of randomized controlled trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized controlled trials</td>
</tr>
<tr>
<td>1c</td>
<td>All or none randomized controlled trials</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or low quality randomized controlled trial</td>
</tr>
<tr>
<td>2c</td>
<td>Outcomes research</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal or based on physiology, bench research, or “first principles”</td>
</tr>
</tbody>
</table>