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Esophageal Cancer

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Cancer Care Alberta

Clinical Practice Guideline GI-009 – Version 6
www.ahs.ca/guru

Background

There are two common distinct histologies of esophageal cancer. Chronic gastroesophageal reflux predisposes to Barrett's metaplasia and the development of adenocarcinoma[1]. Typically, it develops within the distal esophagus; in North America, it is now more prevalent than the other histology, squamous cell carcinoma[2]. The recognized risk factors for squamous cell carcinoma include tobacco and alcohol exposure.[3]

Guideline Questions

1. What are the recommendations for the diagnostic workup of adult patients with esophageal cancer?
2. What are the recommendations for treatment of adult patients with potentially curable esophageal cancer?
3. What are the recommendations for management of adult patients with incurable esophageal cancer?

Search Strategy

This guideline was developed to promote evidence-based practice in Alberta. The following search criteria were used for the 2020 update using the pubmed database: (("oesophageal cancer"[All Fields] OR "esophageal neoplasms"[MeSH Terms] OR ("esophageal"[All Fields] AND "neoplasms"[All Fields]) OR "esophageal neoplasms"[All Fields] OR ("esophageal"[All Fields] AND "cancer"[All Fields]) OR "esophageal cancer"[All Fields]) AND phase[All Fields] AND III[All Fields]) AND (("2016/01/01"[PDAT] : "2019/07/01"[PDAT]) AND "humans"[MeSH Terms]) and ("oesophageal cancer"[All Fields] OR "esophageal neoplasms"[MeSH Terms] OR ("esophageal"[All Fields] AND "neoplasms"[All Fields]) OR "esophageal neoplasms"[All Fields] OR ("esophageal"[All Fields] AND "cancer"[All Fields]) OR "esophageal cancer"[All Fields]) AND "Radiotherapy"[All Fields] AND (("chemoradiotherapy"[MeSH Terms]) OR ("surgery"[All Fields]))

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

Recommended Diagnostic Work-Up

- Esophagogastroduodenoscopy with biopsy establishes the tumour's location (distance from incisors) and histology.
- An augmented CT scan of the thorax, abdomen and pelvis 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.
- if no metastatic disease is seen on the baseline CT, F-fluorodeoxy-D-glucose (FDG) PET scan can complement an augmented CT scan and help to identify radiologically-occult metastatic disease[4-6].

Optional Investigations:

- In the absence of metastatic disease (based upon the above investigations), the following tests may be of additional value if it would influence treatment decisions:
    - Bronchoscopy if tumor is located at or above the level of the carina.[51-53]
    - Endoscopic ultrasound (establishes the depth of penetration into the esophageal wall, invasion into adjacent structures, and involvement of regional and non-regional lymph nodes) for clinically node negative, T1 or T2 tumors.[51-54]
    - Pulmonary function testing (required prior to surgical resection and may be necessary prior to chemoradiotherapy).
- Bone scans can be done for patients suspected of having bone metastases, CT head or MRI for patients suspected of having brain metastases

Stage Information

Tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal rather than gastric cancers. In contrast, EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers (refer to gastric cancer guideline).

Table 1. AJCC Staging System for Esophageal Cancer, Eighth Edition[13].

Definitions	
Depth of Tumour Penetration (T Stage): T_0 No evidence of primary tumor T_{is} Carcinoma *in situ* or high-grade dysplasia T_1 Tumor invades the lamina propria, muscularis mucosae, or submucosa T_{1a} Tumor invades the lamina propria or muscularis mucosae T_{1b} Tumor invades the submucosa T_2 Invasion into muscularis propria T_3 Invasion into adventitia T_4 Tumor invades adjacent structures T_{4a} Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum T_{4b} Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway	**Distant Metastasis (M Stage):** M_0 No distant metastasis M_1 Distant metastasis **Histologic Grade (G Stage):** G_1 Well differentiated G_2 Moderately differentiated G_3 Poorly differentiated, undifferentiated **Location of Squamous Cell Carcinomas:** U Upper esophagus (20 to 25 cm from incisors) M Middle esophagus (>25 to 30 cm from incisors) L Lower esophagus (>30 to 40 cm from incisors) EGJ *Use this staging system if the tumour arises from the esophagogastric junction or from the stomach within 5 cm from esophagogastric junction and crosses the esophagogastric junction. Use the staging system for*

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

*gastric cancer for all other tumours (epicenter in stomach more than 5 cm from the esophagogastric junction and **without** extension into esophagus).*

Squamous Cell Carcinoma (Clinical)

Stage	T	N	M	G	L
Stage 0	is	0	0	NA	NA
Stage I	1	0-1	0	NA	NA
Stage II	2	0-1	0	NA	NA
	3	0	0	NA	NA
Stage III	3	1	0	NA	NA
	1-3	2	0	NA	NA
Stage IV_A	4	0-2	0	NA	NA
Stage IV_B	Any	3	0	NA	NA
Stage IV_C	Any	Any	1	NA	NA

Adenocarcinoma (Clinical)

Stage	T	N	M	G
Stage 0	is	0	0	NA
Stage I	1	0	0	NA
Stage II_A	1	1	0	NA
Stage II_B	2	0	0	NA
Stage III	2	1	0	NA
	3	0-1	0	NA
	4a	0-1	0	NA
Stage IV_A	1-4a	2	0	NA
	4b	0-2	0	NA
	Any	3	0	NA
Stage IV_B	Any	Any	1	NA

Squamous Cell Carcinoma (Pathological)

Stage	T	N	M	G	L
Stage 0	0	0	0	NA	Any
Stage I_A	0	0	1	1	Any
	1a	0	0	X	Any
Stage I_B	1a	0	0	2-3	Any
	1b	0	0	1-3	Any
	1b	0	0	X	Any
	2	0	0	1	Any
Stage II_A	2	0	0	2-3	Any
	2	0	0	X	Any
	3	0	0	Any	L
	3	0	0	1	U/M
Stage II_B	3	0	0	2-3	U/M
	3	0	0	X	Any
	3	0	0	Any	X
	1	1	0	Any	Any
Stage III_A	1	2	0	Any	Any
	2	1	0	Any	Any
Stage III_B	2	2	0	Any	Any
	2	1-2	0	Any	Any
	4a	0-1	0	Any	Any
Stage IV_A	4a	2	0	Any	Any
	4b	0-2	0	Any	Any
	Any	3	0	Any	Any
Stage IV_B	Any	Any	1	Any	Any

Adenocarcinoma (Pathological)

Stage	T	N	M	G
Stage 0	is	0	0	NA
Stage I_A	1a	0	0	1
	1a	0	0	X
Stage I_B	1a	0	0	2
	1b	0	0	1-2
	1b	0	0	X
Stage I_C	1	0	0	3
	2	0	0	1-2
Stage II_A	2	0	0	3
	2	0	0	X
Stage II_B	1	1	0	Any
	3	0	0	Any
Stage III_A	1	2	0	Any
	2	1	0	Any
Stage III_B	2	2	0	Any
	3	1-2	0	Any
	4a	0-1	0	Any
Stage IV_A	4a	2	0	Any
Stage IV_A	4b	0-2	0	Any
Stage IV_A	Any	3	0	Any
Stage IV_B	Any	Any	1	Any

Goals of Therapy

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

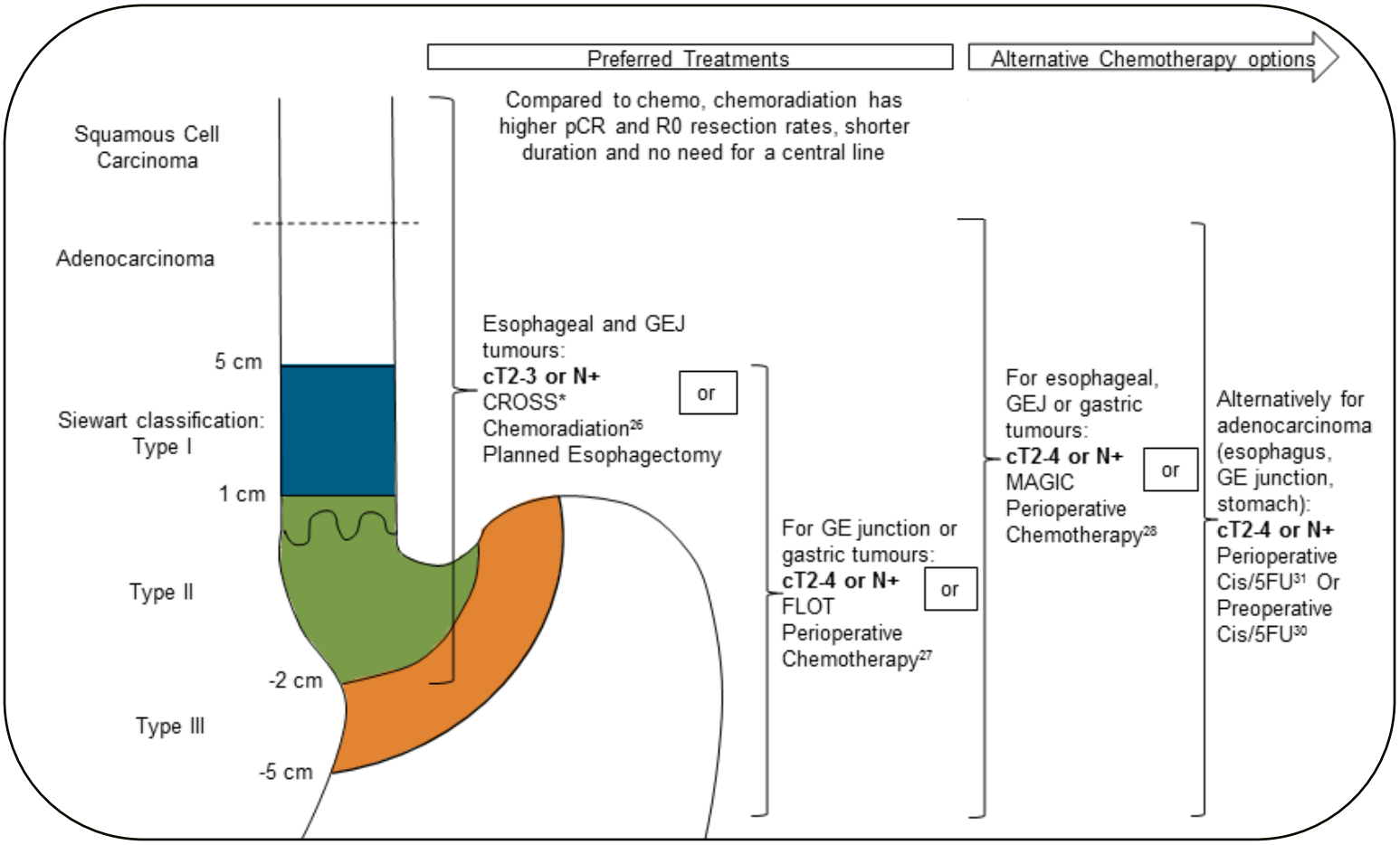
Recommendations[14]:

- Complete the work-up (as described above).
- For patients who do not have metastatic disease:
    - Early referral to a surgeon trained in esophageal surgery is important to assess for resectability.
    - Patients should be referred for a multidisciplinary discussion including radiation oncologists and medical oncologists prior to surgery for patients with resectable disease.
- 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[15].
- Patients who receive preoperative chemoRT should have a CT scan prior to surgery. In certain cases, FDG-PET can provide an assessment of response but should only be done if clinically warranted[7-12].
- There is limited data to support the use of imaging after definitive chemoRT or after surgical resection for non-metastatic patients, however, individualized discussion regarding imaging after definitive chemoRT or after surgical resection for non-metastatic patients may be appropriate in select clinical cases.
- For patients on palliative systemic treatment, CT chest, abdomen, and pelvis should be done every 2-3 months depending on the clinical situation.
- Consider treatment on a clinical trial, if available.

Table 2. Modified dysphagia score.

Modified Dysphagia Score[16]	
0	Ability to eat normal diet
1	Ability to eat some solid food
2	Ability to eat semisolids only
3	Ability to swallow liquids only
4	Complete dysphagia

Figure 1: Operable esophagogastric cancer clinical stage II-III[17-21].



* Multidisciplinary discussion regarding chemoRT vs chemotherapy recommended
For gastric cancers, refer to the Gastric Cancer Guidelines.
For more details, refer to table 2.
Note: EGJ was redefined in the AJCC 8th edition: adenocarcinomas with epicenters no more than 2cm into the gastric cardia are staged as esophageal adenocarcinomas, and those extending further are staged as stomach cancers.[55]

Table 3. Curative therapy recommendations for patients with esophageal cancer.

Stage	Recommendations	
$T_{is}N_0$ or $T_{1a}N_0$ Disease	Preferred	**Endoscopic Therapy for Superficial Cancers:** • Endoscopic mucosal resection (EMR)[22], submucosal dissection (ESD) and various ablation techniques (e.g.: photo-dynamic therapy[23], argon plasma coagulation, radiofrequency ablation[24] , cryotherapy) can preserve the integrity of the esophagus and provide a potentially curative option for superficial cancers. • Provided careful endoscopic surveillance can be performed, consider for patients with favorable mucosal tumours* who are interested in an esophagus-sparing approach or who are elderly, with multiple comorbidities, or otherwise high surgical risk. ***Note**: Favorable mucosal tumours include non-invasive (*in situ*) lesions or disease that invades into the mucosa (but *not* submucosa).

<table>
<tr><td></td><td>Alternate</td><td>
<table>
<tr><th>Stage</th><th>Description</th><th>Chance of Lymph Node Involvement</th></tr>
<tr><td>$T_{is\ (m1)}$</td><td>Presence in the epithelial layer of the mucosa</td><td>0%</td></tr>
<tr><td>$T_{1a\ (m2)}$</td><td>Invasion into lamina propria mucosal</td><td>0%</td></tr>
<tr><td>$T_{1a\ (m3)}$</td><td>Invasion into (not through) muscularis mucosae</td><td>7%</td></tr>
<tr><td>$T_{1b\ (sm1)}$</td><td>Invasion into superficial third of submucosa</td><td>15%</td></tr>
<tr><td>$T_{1b\ (sm2)}$</td><td>Invasion into middle third of submucosa</td><td>27%</td></tr>
<tr><td>$T_{1b\ (sm3)}$</td><td>Invasion into deepest third of submucosa</td><td>49%</td></tr>
</table>
Esophagectomy:
• Resect disease if both technically and medically feasible. Aim to achieve an “R_0“resection (no gross or microscopic residual tumour).
• Post-operative morbidity and survival are significantly better when surgery is completed in an experienced centre[25].</td></tr>
<tr><td>$T_{1b}N_0$ Disease</td><td>Preferred</td><td>Esophagectomy:
• Esophagectomy is the preferred treatment choice for fit patients with superficial esophageal cancers invading the submucosa.</td></tr>
<tr><td></td><td>Alternate</td><td>Endoscopic therapy:
• For most patients with favorable intramucosal tumors, who are interested in an esophagus-sparing approach or are older with multiple comorbidities or are otherwise high surgical risk are candidates for endoscopic resection rather than surgical resection.
• If a patient is not medically operable, declines surgery, or is not a candidate for EMR/ESD, refer to Table 3</td></tr>
<tr><td>T_2, T_3, N_+, M_0 Disease*</td><td>Preferred</td><td>Pre-Operative Chemoradiotherapy followed by Esophagectomy (if possible):
• CROSS pre-operative chemoradiation (Level 1 evidence): Deliver 4,140 cGy in twenty-three fractions over five weeks plus Paclitaxel 50 mg/m^2 IV and Carboplatin AUC 2 IV on days 1, 8, 15, 22, and 29 [17]. This protocol improves the R_0 resection rate (92% versus 69%) and overall survival (HR 0.657, $CI_{95\%}$ 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.
• Aim to achieve an “R_0“resection (no gross or microscopic residual tumour).
• Post-operative morbidity and survival are significantly better when surgery is completed in an experienced centre[25].
•Post-operative Adjuvant Therapy:
The Checkmate 577 trial randomized patients who received preoperative CROSS chemoradiotherapy followed by surgery with residual pathological disease (> ypT1 and/or >ypN1) to nivolumab (240 mg/m^2 IV q 2 weekly for up to 1 year) or placebo.</td></tr>
</table>

*Note that esophagectomy alone is an option in low risk cT2N0 patients.[56]

		Disease free survival (DFS) was significantly improved in the nivolumab group compared to the placebo (median 22.4 months versus 11.0 months, HR 0.69, 95% CI 0.56-0.86, p=0.003).[48] Nivolumab is not currently funded for this indication in Alberta. • No randomized trial (and at least two meta-analyses [26,27] has demonstrated a survival advantage for preoperative chemoradiotherapy over chemotherapy alone • One network meta-analysis concluded that there is a survival benefit for neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy [28]. o 31 randomized controlled trials involving 5496 patients were included in the quantitative analysis o Neoadjuvant chemoradiotherapy improved overall survival when compared to all other treatments including: o Surgery alone (HR 0.75, 95% CI 0.67-0.85) o Neoadjuvant chemotherapy (HR 0.83, 95% CI 0.70-0.96) and o Neoadjuvant radiotherapy (HR 0.82, 95% CI 0.67-0.99) • In the neoadjuvant setting, treatment with chemoradiotherapy yields higher rates of pCRs and R0 resections compared to chemotherapy. Chemoradiation is also of shorter duration and there is no need for a central line. Decisions regarding the optimal neoadjuvant therapeutic modality warrants a multidisciplinary discussion incorporating the planned surgery, tumor anatomy, patient wishes and comorbidities.
T_2, T_3, or T_{4a} N_+, M_0 Disease	Chemotherapy	**Peri-Operative Chemotherapy:** **Preferred:** FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel, (Level 1 evidence) was superior to epirubicin, cisplatin and fluorouracil /capecitabine for resectable cT2 or cN1+ gastric and gastroesophageal adenocarcinomas. Patients with Siewart type 1 to 3 gastroesophageal adenocarcinoma comprised 56% of patients in the trial. Median survival with FLOT was 50 months versus 35 months with ECF/ECX HR 0.77(, $CI_{95\%}$ 0.63-0.94, p =0.012)[18]. • Perioperative chemotherapy with FLOT consists of 4 cycles of chemotherapy prior to surgery with a further 4 cycles of chemotherapy post-surgery. Each cycle lasts 14 days and consists of 5-FU 2600 mg/m^2 (24 h) day 1 and leucovorin 200 mg/m^2 (2h), day 1 and oxaliplatin 85 mg/m^2 (2 h) day 1 and docetaxel 50 mg/m^2 (1 h), every 2 weeks. Prophylactic GCSF should be considered for patients undergoing FLOT, as grade 3/4 neutropenia occurs at a higher rate than ECF/ECX. **Note:** The FLOT trial did not include esophageal cancers. **Alternatives for patients not candidates for FLOT** • MAGIC: When compared to surgery alone in patients with good performance status (ECOG ≤1) and $T_{2\text{-}4}N_{0\text{-}3}M_0$ 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, $CI_{95\%}$ 0.53-0.81, $p < 0.001$) and overall survival (from 23.0% to 36.3%, HR 0.74, $CI_{95\%}$ 0.59-0.93, $p = 0.008$[19]). · *Pre-Operative Phase:* Three three-week cycles of Epirubicin 50 mg/m^2 and Cisplatin 60 mg/m^2 IV on day one plus a continuous intravenous infusion of 5-Fluorouracil 200 mg/m^2/day over twenty-one days.

		· *Operative Phase:* Perform surgical resection with oncologic principles. · *Post-Operative Phase:* As described in the pre-operative phase (above). **Alternative for patients not candidates for epirubicin (MAGIC):** cisplatin 5FU has been evaluated in patients with operable adenocarcinoma of the esophagus and gastroesophageal junction • The FFCD trial six peri-operative cycles of Cisplatin and infusional fluorouracil improves the five-year disease-free survival (34% *versus* 19%, HR 0.65, $CI_{95\%}$ 0.48-0.89, *p* = 0.003), overall survival (38% *versus* 24%, HR 0.69, $CI_{95\%}$ 0.50-0.95, *p* = 0.02), and rate of curative resection (84% *versus* 73%, *p* = 0.04) compared to surgery alone. Chemotherapy was given every 4 weeks and was comprised of cisplatin 100 mg/m^2 IV on day one plus 5-Fluorouracil 800 mg/m^2/day over days one through five days, every 28 days[29]. • The OE5 trial randomized patients to 4 cycles of ECX or 2 cycles of cisplatin and infusional fluorouracil prior to surgery. The pathological complete response rate was higher in the ECX arm compared to cisplatin/fluoruracil (11% vs 3%). However, there was no significant difference in overall survival (23.4 months vs 26.1 months, HR 0.90 0.77-1.05, p = 0.19)[21] • These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port. • For patients in whom it is not possible to resect disease due to medical or technical issues, refer to Table 3

Table 3. Recommendations for patients with esophageal cancer who are not candidates for surgery.

Stage	Recommendations	
$T_{1-4}N_{0-3}$	Preferred Recommendation	In whom it is not possible to resect disease due to medical or technical issues: **Primary ('Definitive') Chemoradiotherapy:** • The two treatment options are: • **Preferred:** Deliver 5,000 cGy in twenty-five fractions over five weeks plus Oxaliplatin 85 mg/mg^2 IV and Leucovorin 200 mg/m^2 IV followed by 5-Fluorouracil 400 mg/m^2 IV bolus followed by 5-Fluorouracil 800 mg/m^2/day over days one and two on weeks one, three, five, seven, nine, and eleven. 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 [30]. (Level 1 evidence) • **Alternatively** deliver 5,000 cGy in twenty-five fractions over five weeks plus Cisplatin 75 mg/m^2 IV over one hour and 5-Fluorouracil 4,000 mg/m^2 IV over ninety-six hours on weeks one, five, eight, and eleven. This protocol offers an five-year overall survival rate of 27% (compared to 0% for radiotherapy alone)[31]. **Note**: 82% of the patients enrolled had squamous cell carcinoma of the esophagus. • These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port.
	Alternate	Radiotherapy Alone: • Consider for patients who decline chemotherapy or in whom chemotherapy is deemed unsafe.

Recommendations for Incurable Situations

Provide palliative maneuvers to maintain and/or improve quality of life:

1. Relieve pain, bleeding, and/or dysphagia with radiotherapy (30 Gy in 10 fractions is preferred, alternatively 40 Gy in 15 fractions or 50 Gy in 20 fractions).
2. Consider placement of an endoluminal stent[32,33]or photodynamic therapy[34] to relieve dysphagia.
3. Patients with advanced esophageal cancer who have a self expanding metal stent inserted for the primary management of dysphagia do not gain additional benefit from concurrent palliative radiotherapy (Level 1 evidence). Palliative radiotherapy may be indicated for bleeding.[49]
4. Consider palliative chemotherapy to control disease and prolong survival in patients with a satisfactory performance status (ECOG ≤ 2)[35-41]
5. Consider treatment on a clinical trial if available.
6. Consider early referral to palliative care. (Symptom management guidelines can be found here).
7. Refer to dieticians and consider psychosocial referral. Early interdisciplinary care with the addition of psychologists and dieticians improved survival compared to standard oncology care in phase III trial of untreated patients with metastatic upper GI cancers (median overall survival 14.8 months vs 11.9 months, HR 0.68; 95% CI 0.51-0.9,; = 0.021).[58]

Table 4. ECOG Performance Status Scale.

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

Metastatic Adenocarcinoma of the Esophagus or Gastroesophageal Junction

Many phase III clinical trials for metastatic gastric cancer also included patients with adenocarcinoma of the gastroesophageal junction. By extrapolation, patients with metastatic adenocarcinoma of the esophagus and gastroesophageal junction are treated as per metastatic gastric cancers. [Link to Gastric Guideline].

Evaluation of HER2 protein expression via immunohistochemistry or in situ hybridization is recommended to select patients with metastatic esophageal/gastroesophageal adenocarcinoma for trastuzumab based treatment[42].

Metastatic Squamous Cell Cancer of the Esophagus

There is limited data to guide systemic therapy for metastatic squamous cell cancer of the esophagus. The combination of a platinum with a fluoropyrimidine is the preferred first line regimen[42,43].

- Patients with squamous cell esophageal cancer comprised approximately 10% of patients in the REAL-2 trial. Capecitabine-based combination regimens (e.g.: ECX, EOX, CX) offer a superior response rate (45.6% *versus* 38.4%, OR 1.38, $CI_{95\%}$ 1.10-1.73, $p = 0.006$) and overall survival (HR 0.87, $CI_{95\%}$ 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%[33]. It is administered in three-week cycles where Epirubicin (50 mg/m^2 IV over twenty minutes) and Cisplatin (60 mg/m^2 IV over one hour along with hydration) are administered on day one. Capecitabine (625 mg/m^2 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/m^2/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)[44]. They undermine overall survival (7.4 months *versus* 10.5 months, HR 0.80, $CI_{95\%}$ 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, $CI_{95\%}$ 0.78-0.99, $p = 0.04$), progression (HR 0.88, $CI_{95\%}$ 0.80-0.98, $p = 0.02$), and thromboembolism[45].
- Oxaliplatin based chemotherapy is a reasonable option. A phase II trial evaluated FOLFOX (100) in metastatic squamous cell cancer of the esophagus. The response rate was 23.2% with a median overall survival of 7.7 months[46].

- *Preliminary data from the KEYNOTE-590 trial has demonstrated promising results. The trial randomized patients with advanced esophageal carcinoma (adenocarcinoma or squamous, N=749) to Pembrolizumab plus cisplatin/infusional 5FU chemotherapy versus chemotherapy alone. After a median follow-up of 10.8 months, Pembrolizumab + chemo demonstrated superior OS in ESCC patients (median OS 12.6 mo vs. 9.8 mo; HR: 0.72; 95%CI: 0.43-0.75; p<0.001). The benefit was seen in all patients, but primarily driven by the patients with squamous cell cancer.[50] Pembrolizumab is not currently funded for this indication in Alberta.*

Second Line Therapy[47]

The ATTRACTION-3 study randomized patients with advanced esophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy to nivolumab versus chemotherapy of physician's choice (paclitaxel 100 mg/m2 q week for 6 weeks followed by 1 week off) or docetaxel (75 mg/m2 q3 weeks). Overall survival was significantly improved in the nivolumab group compared to chemotherapy (median 10.9 months versus 8.4 months, HR 0.77, 95% CI 0.62-0.96; p=0.019). There was no significant difference in progression free survival for nivolumab versus chemotherapy (median 1.7 months versus 3.4 months, HR 1·08, 95% CI 0·87–1·34). The prespecified interaction analysis indicated no significant interaction of treatment effect by PD-L1 status. Nivolumab is not currently available on the Alberta CancerCare Drug Benefit List.

Taxane based chemotherapy would be a reasonable alternative option and is available through the Alberta CancerCare Drug Benefit List.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta GI Tumour Team. Members of the Alberta GI Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, gastroenterologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta GI Tumour Team, external participants identified by the Working Group Lead, 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 2010.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AJCC, American Joint Committee on Cancer; CF, cisplatin + 5-fluorouracil; CI, confidence interval; CT, computed tomography; CVC, central venous catheter; CX, cisplatin + Capecitabine; ECF, epirubicin + cisplatin + 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; ECX, epirubicin + cisplatin + Capecitabine; EMR, endoscopic mucosal resection; EOF, epirubicin + oxaliplatin + 5-fluorouracil; EOX, epirubicin + oxaliplatin + Capecitabine; FDG-PET, fluorodeoxy-D-glucose positron emission tomography; HR, hazard ratio; IV, intravenous; NG, nasogastric; OR, odds ratio; pCR, pathological complete response; PICC, peripherally inserted central catheter; TNM, tumour-node-metastasis.

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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Conflict of Interest Statements

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