Esophageal Cancer

Thoracic Practice Guideline

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Esophageal Cancer

Background: incidence, risk factors, survival rate, treatment and diagnostics

The incidence of esophageal cancer has risen in recent decades, coinciding with a shift in histologic type and primary tumor location. [2,3] Adenocarcinoma of the esophagus is now more prevalent than squamous cell carcinoma in the United States and western Europe, with most tumors located in the distal esophagus. The cause for the rising incidence and demographic alterations is unknown.

While risk factors for squamous cell carcinoma of the esophagus have been identified (e.g., tobacco, alcohol, diet), the risk factors associated with esophageal adenocarcinoma are less clear.[3] The presence of Barrett esophagus is associated with an increased risk of developing adenocarcinoma of the esophagus, and chronic reflux is considered the predominant cause of Barrett metaplasia. The results of a population-based, case-controlled study from Sweden strongly suggest that symptomatic gastroesophageal reflux is a risk factor for esophageal adenocarcinoma. The frequency, severity, and duration of reflux symptoms were positively correlated with increased risk of esophageal adenocarcinoma. [4]

Esophageal cancer is a treatable disease, but it is rarely curable. The overall 5-year survival rate in patients amenable to definitive treatment ranges from 5% to 30%. The occasional patient with very early disease has a better chance of survival. Patients with severe dysplasia in distal esophageal Barrett mucosa often have in situ or even invasive cancer within the dysplastic area. Following resection, these patients usually have excellent prognoses.

Primary treatment modalities include surgery alone or chemotherapy with radiation therapy. Combined modality therapy (i.e., chemotherapy plus surgery, or chemotherapy and radiation therapy plus surgery) is under clinical evaluation. Effective palliation may be obtained in individual cases with various combinations of surgery, chemotherapy, radiation therapy, stents, [5] photodynamic therapy,[6-8] and endoscopic therapy with Nd:YAG laser.[9]

One of the major difficulties in allocating and comparing treatment modalities for patients with esophageal cancer is the lack of precise preoperative staging. Standard noninvasive staging modalities include computed tomography (CT) of the chest and abdomen, and endoscopic ultrasound (EUS). The overall tumor depth staging accuracy of EUS is 85% to 90%, as compared with 50% to 80% for CT; the accuracy of regional nodal staging is 70% to 80% for EUS and 50% to 70% for CT.[10,11] EUS-guided fine-needle aspiration (FNA) for lymph node staging is under prospective evaluation; one

retrospective series reported a 93% sensitivity and 100% specificity of regional nodal staging with EUS-FNA.[12] Thoracoscopy and laparoscopy have been used in esophageal cancer staging at some surgical centers.[13-15] An intergroup trial reported an increase in positive lymph node detection to 56% of 107 evaluable patients using thoracoscopy/laparoscopy, from 41% (using noninvasive staging tests, e.g., CT, magnetic resonance imaging, EUS) with no major complications or deaths.[16] Noninvasive positron emission tomography using the radiolabeled glucose analog 18-F-fluorodeoxy-D-glucose for preoperative staging of esophageal cancer is under clinical evaluation and may be useful in detecting stage IV disease.[17-20]

Gastrointestinal stromal tumors can occur in the esophagus and are usually benign.

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Pathology: Cellular Classification

Fewer than 50% of esophageal cancers are squamous cell carcinomas. Adenocarcinomas, typically arising in Barrett esophagus, account for at least 50% of malignant lesions, and the incidence of this histology appears to be rising. Barrett esophagus contains glandular epithelium cephalad to the esophagogastric junction.

Three different types of glandular epithelium can be seen:

* Metaplastic columnar epithelium.
* Metaplastic parietal cell glandular epithelium within the esophageal wall.
* Metaplastic intestinal epithelium with typical goblet cells.

Dysplasia is particularly likely to develop in the intestinal type mucosa.

Gastrointestinal stromal tumors can occur in the esophagus and are usually benign.

Staging

The stage determines whether the intent of the therapeutic approach will be curative or palliative. The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.[1]
TNM definitions

Primary tumor (T)

* TX: Primary tumor cannot be assessed
* T0: No evidence of primary tumor
* Tis: Carcinoma in situ
* T1: Tumor invades lamina propria or submucosa
* T2: Tumor invades muscularis propria
* T3: Tumor invades adventitia
* T4: Tumor invades adjacent structures

Regional lymph nodes (N)

* NX: Regional lymph nodes cannot be assessed
* N0: No regional lymph node metastasis
* N1: Regional lymph node metastasis

Distant metastasis (M)

* MX: Distant metastasis cannot be assessed
* M0: No distant metastasis
* M1: Distant metastasis
    - Tumors of the lower thoracic esophagus:
        + M1a: Metastasis in celiac lymph nodes
        + M1b: Other distant metastasis
    - Tumors of the midthoracic esophagus:
        + M1a: Not applicable
        + M1b: Nonregional lymph nodes and/or other distant metastasis
    - Tumors of the upper thoracic esophagus:
        + M1a: Metastasis in cervical nodes
        + M1b: Other distant metastasis

For tumors of the midthoracic esophagus, use only M1b because these tumors with metastases in nonregional lymph nodes have equally poor prognoses as do those with metastases in other distant sites.
AJCC stage groupings

Stage 0

* Tis, N0, M0

Stage I

* T1, N0, M0

Stage IIA

* T2, N0, M0
* T3, N0, M0

Stage IIB

* T1, N1, M0
* T2, N1, M0

Stage III

* T3, N1, M0
* T4, any N, M0

Stage IV

* Any T, any N, M1

Stage IVA

* Any T, any N, M1a

Stage IVB

* Any T, any N, M1b

The current staging system for esophageal cancer is based largely on retrospective data from the Japanese Committee for Registration of Esophageal Carcinoma. It is most applicable to patients with squamous cell carcinomas of the upper third and middle third of the esophagus, as opposed to the increasingly common distal esophageal and gastroesophageal junction adenocarcinomas. [2] In particular, the classification of involved abdominal lymph nodes as M1 disease has been criticized. The presence of positive abdominal lymph nodes does not appear to carry as grave a prognosis as metastases to distant organs.[3] Patients with regional and/or celiac axis lymphadenopathy should not necessarily be considered to have unresectable disease caused by metastases. Complete resection of the primary tumor and appropriate lymphadenectomy should be attempted when possible.

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Treatment Options

Stage 0 Esophageal Cancer and Severe Dysplasia

Stage 0 esophageal cancer is rarely seen in Canada, but surgery has been used for this stage of cancer. [1, 2]

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Stage I Esophageal Cancer

Standard treatment options:

- Surgery.[1,2]

Stage IIA Esophageal Cancer

Standard treatment options at LRCP:

- Surgery.[1,2]

Treatment options:

- Chemotherapy plus radiation therapy with or without subsequent surgery.[3-6]
- Chemotherapy with subsequent surgery.[6]
    - See next section for chemotherapy and radiotherapy details.

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Stage IIB and Stage III Esophageal Cancer

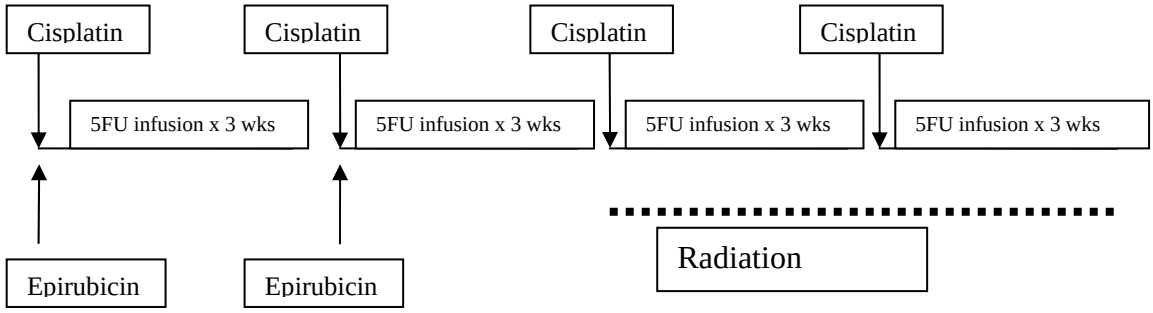
Standard treatment options:

1. Surgical resection.[1,2]
2. Surgical resection followed by chemoradiation. [3]
3. Induction chemoradiation followed by surgery.[4]
4. Induction chemotherapy followed by surgery.[4]
5. Chemotherapy plus radiation [5,6]

Chemotherapy usually involves epirubicin, cisplatin and 5-fluorouracil. However, the exact chemotherapy regimen used depends on

- Timing of therapy (induction or adjuvant)
- Radiation (sequential or concurrent)

A. Adjuvant Treatment (Item #2 above) or Definitive Therapy (Item #5 above)
    a. ECF chemotherapy is given for two cycles, plus two cycles of CF concurrently with radiation



Cisplatin (Platinol7, Platinol-AQ7)

Cisplatin 60 mg/m2 bolus IV (in a 500 mL bag) infusion over 30 minutes on days 1 and 22 with prehydration, other standard renal-protective measures, and appropriate antiemetic coverage. The following is recommended:

Prior to cisplatin, begin intravenous hydration with 1,000 mL normal saline IV over 2 hours. Furosemide 40 mg IV in a 50 mL mini bag with hydration.

Anti-emetics include: dexamethasone 4 mg po q12h for 7 doses starting the morning of chemotherapy; ondansetron 8 mg po q12h for 7 doses starting the morning of chemotherapy; prochlorperazine 10 mg po q4h prn.

After the cisplatin infusion, complete the remaining 500 ml of normal saline IV hydration over 2 hours. The patient should be encouraged to drink as much liquid as possible overnight.

5-Fluorouracil (5-FU, fluorouracil, Efudex7, Adrucil7)

5-Fluorouracil 200 mg / m^2 / day continuous for 7 days after completion of cisplatin infusion (days 1-7). The infusion will be repeated for 2 additional weeks on days 8-14 and 15-21. (Total 5-FU dose per cycle is 600 mg / m^2) The cycle will be repeated on day 22. The CIV 5FU will thus continue for a total of 12 weeks and until the radiation is completed, barring dose adjustments due to toxicities.

Epirubicin

Epirubicin 50 mg / m^2 IV bolus will be given on days 1 and 22. Because of significant radiosensitizing toxicities of Epirubicin, the drug will be withheld during radiation treatment.

Radiation Therapy is to start at the first day of the 3rd cycle of chemotherapy. The total dose is 50.4Gy (1.8Gy/fx/day), 5 days a week.

B. Neoadjuvant therapy (Item #3 above)
    a. Cisplatin and short-term (96-hour) 5FU infusion are given for two cycles, during weeks 1 and 5 of radiation

Cisplatin (Platinol7, Platinol-AQ7)

Cisplatin 25 mg/m2 bolus IV (in a 500 mL bag) infusion over 30 minutes on days 1 and 2 and 3 and possibly (if patient has good performance status) day 4 for a total dose of 75 – 100 mg/m^2 with prehydration, other standard renal-protective measures, and appropriate antiemetic coverage.

This dosing is repeated with the start of week 5 of radiation (i.e. day 29)

The following is recommended:

Prior to cisplatin, begin intravenous hydration with 1,000 mL normal saline IV over 2 hours. Furosemide 40 mg IV in a 50 mL mini bag with hydration.

Anti-emetics include: dexamethasone 4 mg po q12h for 7 doses starting the morning of chemotherapy; ondansetron 8 mg po q12h for 7 doses starting the morning of chemotherapy; prochlorperazine 10 mg po q4h prn;.

After the cisplatin infusion, complete the remaining 500 ml of normal saline IV hydration over 2 hours. The patient should be encouraged to drink as much liquid as possible overnight.

5-Fluorouracil (5-FU, fluorouracil, Efudex7, Adrucil7)

5-Fluorouracil 1000 mg / m^2 / day continuous for four days. The infusion will be repeated on days 29-32. (Total 5-FU dose per infusion is 4000 mg / m^2)

Radiation Therapy is to start at the first cycle of chemotherapy. The total dose is 50.4 Gy (1.8 Gy/fx/day), 5 days a week.

C. Single modality chemotherapy followed by surgery (without concurrent radiation) (Item #4 above)
    a. Four cycles of ECF chemotherapy can be used (see under A) above), ie. Including epirubicin with all four cycles if tolerated

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Stage IV Esophageal Cancer

At diagnosis, approximately 50% of patients with esophageal cancer will have metastatic disease and will be candidates for palliative therapy.[1]

Stage IVA that consists of resectable disease and resectable celiac nodes

Standard treatment options:

- Surgical resection.[10,11]
- Surgical resection followed by chemoradiation. [12]
- Induction chemoradiation followed by surgery.[13]
- Induction chemotherapy followed by surgery.[13]
- Chemotherapy plus radiation [14,15]

Stage IVA with unresectable bulky celiac nodes and all IVB patients

Standard treatment options:

1. Endoscopic-placed stents to provide palliation of dysphagia.[2]
2. Radiation therapy with or without stents.
3. Intraluminal brachytherapy to provide palliation of dysphagia.[3,4]
4. Nd:YAG endoluminal tumor destruction or electrocoagulation.[5]
5. Chemotherapy has provided partial responses for patients with metastatic distal esophageal adenocarcinomas.[6-8]
    a. Four cycles of ECF chemotherapy can be used ie. Including epirubicin with all four cycles if tolerated
    b. In the palliative setting, modifications are used to take patient performance status and tumour response into account, for example
        i. Continuing beyond four cycles or stopping earlier
        ii. Modifying dose
        iii. Substituting carboplatinum for cisplatinum

Many agents are active in esophageal cancer. Objective response rates of 30% to 60% and median survivals of less than 1 year are commonly reported with platinum-based combination regimens with fluorouracil, taxanes, topoisomerase inhibitors, hydroxyurea, or vinorelbine.[1,8,9]

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Recurrent Esophageal Cancer

All recurrent esophageal cancer patients present difficult problems in palliation. All patients, whenever possible, should be considered candidates for clinical trials as outlined in treatment overview.

Standard treatment options:

- Palliative use of any of the standard therapies, including supportive care.

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This guideline is a statement of consensus of the Thoracic Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.