PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GASTROINTESTINAL

ESOPHAGEAL CANCER
GI Site Group – Esophageal cancer

Authors: Dr. Jennifer Knox, Dr. Mairead McNamara
Updated: Dr. Rebecca Wong, Dr. Gail Darling, Dr. Carol Swallow

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These guidelines are evidence-based and thus subject to change. Some recommendations are currently funded in this jurisdiction, while others are in negotiation.

1. Introduction

During the past two decades, the incidence of squamous cell cancers of the esophagus has decreased, although the incidence of adenocarcinomas of the esophagus and gastroesophageal junction is continuing to increase rapidly and is now the predominant cell type in North America and Western Europe. At University Health Network (UHN), adenocarcinoma represents approximately 75% of new cases of esophageal cancer. Areas of high incidence include portions of Iran, Russia, and Northern China where squamous cell cancers dominate. The disease is less common in Japan, Europe, the United States and Canada.

The main risk factors for squamous cell carcinomas in Western countries are smoking and alcohol consumption, whereas risk factors for adenocarcinomas include obesity, severe, prolonged gastroesophageal reflux disease (GERD) with or without Barrett’s esophagus, male sex, smoking (but not alcohol), increasing age and white or Hispanic race.

2. Screening and early detection

It is unclear if rigorous medical management of reflux disease with long-term proton pump inhibitors can affect the natural history of the disease or the development of the subsequent malignant process.

The typical treatment for patients with Barrett’s esophagus is surveillance using upper endoscopy and biopsy to examine tissue for evidence of dysplasia. Radiofrequency ablation is accepted treatment for Barrett’s esophagus with high grade dysplasia.

3. Diagnosis

Diagnostic workup should include:

(1) Clinical examination, blood counts, liver, pulmonary and renal function tests.

(2) Endoscopy and biopsy. In patients planned for surgical resection, endoscopic ultrasound (EUS) is required to evaluate T and N stage of tumour.

(3) CT scan chest/abdomen/pelvis.

(4) In patients planned for surgical resection, positron emission tomography (PET)/CT to determine node status and occult sites of distant metastatic spread should be considered if funding permits.
(5) In locally advanced (T3/T4) adenocarcinomas of the esophago-gastric junction infiltrating the anatomic cardia, laparoscopy can be used at surgeons’ discretion to rule out peritoneal metastases. This is predominantly considered for cancer of gastric origin if indicated.

4. Pathology

Small cell carcinomas, lymphomas, sarcomas, neuroendocrine primaries, which are very uncommon, must be identified and separated from squamous cell carcinomas and adenocarcinomas and be treated accordingly, and therefore pathology review is paramount.

Staging: The American Joint Committee on Cancer (AJCC) TNM staging (Esophageal carcinoma) is available online at www.nccn.org. The Union for International Cancer Control (UICC) TNM staging (Esophageal carcinoma) differs slightly. The AJCC system adopted the use of post neoadjuvant stage groupings (ypTNM) but not adopted by UICC. Important Features in the 8th edition include nodal staging: N1: 1-2 nodes, N2: 3-5 nodes, N3: > 6 nodes. The regional nodes for all locations extend from periosophageal cervical nodes to celiac nodes. Cancers involving the EGJ that have their epicenter within 2 cm from the EGJ is staged are esophagus carcinoma.

5. Management

5.1 Surgery

Surgery is the treatment of choice in early esophageal cancer (Tis-T1aN0). Endoscopic resection is a treatment option for selected patients with high grade dysplasia or intramucosal cancer without invasion of the submucosa and shows equal cure rates in specialized centres (Ell al., 2007). For T1b lesions, endoscopic resection can be considered if significant comorbidities.

Surgery alone can be regarded as standard treatment of localized disease (T1-2 N0-1 M0), although long-term survival does not exceed 25% if regional lymph nodes are involved and post-operative systemic treatment should be considered in node positive disease. T2N0M0 may be managed with primary surgery although this is becoming more controversial with the recognition that true T2N0 is rare and 60-75% of patients with T2 disease have nodal metastases.

Transthoracic esophagectomy with two-field lymph node resection and a gastric tube anastomosed in the left neck is recommended for esophageal cancer of the mid or distal third of the esophagus and gastroesophageal junction regardless of histology. Open transthoracic, minimally invasive or transhiatal techniques are acceptable (Omloo et al., 2007). Regardless of approach, adequate lymphadenectomy is recommended and can include both upper abdominal nodes (D1 or D1+) and lower mediastinal lymph nodes. Inclusion of the third field lymph node dissection of the lower cervical and recurrent...
laryngeal or supraclavicular nodes is controversial but may be considered for mid or upper third cancers. Proximal and distal margins should be at least 5 cm above and below the tumour. Cancers of the gastric cardia involving the gastroesophageal junction may be resected with esophagogastrectomy. No standard treatment can be identified for carcinomas of the cervical esophagus; concurrent chemotherapy/radiotherapy is favoured and patients with this diagnosis are usually treated by head and neck specialists in the University Health Network and are addressed in policies from that group. Surgery has been reserved as a salvage procedure but requires both esophagectomy and laryngectomy.

5.2.1 Chemotherapy/Radiotherapy

Trimodality therapy rather than surgery alone is recommended for patients with T2-3 N0 and all patients with stages IIA, IIB and III thoracic esophageal cancer regardless of histology.

Concurrent chemoradiotherapy instead of chemotherapy or radiotherapy alone is recommended for neoadjuvant therapy. Low dose weekly carboplatin (area under the curve of concentration X time [AUC] 2) plus weekly paclitaxel 50 mg/m² plus concurrent radiotherapy (41.4 Gy over five weeks) regimen as was used in the Dutch CROSS trial (van Hagen et al., 2012) is the standard approach. For patients with borderline resectability, cisplatin 100 mg/m² plus 5-FU 1000 mg/m²/day for 4 days on weeks 1 and 5 concurrent with radiotherapy (50.4 Gy total: 1.8 Gy/fraction over 5.6 weeks) as was used in CALGB 9781 (Tepper et al., 2008) is preferred, delivering a radiotherapy dose fractionation that is consistent with radical chemoradiotherapy. The CROSS study reports better tolerability than previous reports and has very acceptable peri-operative complication rates in one of the largest randomized trials in esophageal cancer. The role of newer chemotherapy drugs combined with radiotherapy is being investigated.

Definitive chemoradiotherapy is a standard treatment option especially for patients who are not surgical candidates or in patients who do not wish to undergo surgical resection. In the RTOG trial (Herskovic et al., 1992) established the use of chemoradiotherapy as superior when compared with radiotherapy alone. In this study, patients received two cycles of infusional 5-FU (1000 mg/m² per day, days 1 to 4, weeks 1 and 5) plus cisplatin (75 mg/m² day 1 of weeks 1 and 5) and radiotherapy (50 Gy in 25 fractions over 5 weeks) in patients with locoregional thoracic esophageal cancer, with an additional two cycles of chemotherapy three weeks apart after radiotherapy. For patients with squamous cell carcinoma, definitive chemoradiotherapy is non-inferior to chemoradiotherapy and surgery (Stahl et al 2005, Bedenne et al 2007). If salvage surgery is a potential option, patients should be followed by regular surveillance including endoscopy and anatomical imaging (Vincent et al 2015).

Dose escalation beyond 50Gy in 25 fr can be considered at the discretion of the treating oncologist in patients where surgical salvage is unlikely ever to be an option (Brower 2016, Luo et al 2018). This can be accomplished using either external beam boost or brachytherapy. When brachytherapy is used, care should be taken to ensure adequate recovery of acute chemotherapy toxicity since toxic deaths have been described when brachytherapy is used with concomitant chemotherapy.
Induction chemotherapy without radiotherapy has been adopted in the United Kingdom for esophagogastric junction (EGJ) adenocarcinomas based upon results of the MAGIC trial (Cunningham et al., 2006) but whether these results can be extrapolated to the setting of esophageal squamous cell carcinomas is unknown.

For patients with completely resected node-positive esophageal cancer who have not received neoadjuvant therapy, postoperative adjuvant therapy such as chemotherapy alone (Cisplatin/5-FU (Ando et al., 2003) or Cisplatin/Paclitaxel (Armanios et al., 2004)) are reasonable options. ECF could also be considered.

Post operative chemoradiotherapy can be considered in patients at high risk of local regional recurrence but is not Princess Margaret Cancer Centre policy.

5.2.2 Treatment of metastatic disease - First line chemotherapy

The treatment of advanced esophageal and gastric cancers has converged and the majority of patients with gastric, esophageal, or esophagogastric junction cancers are treated similarly, regardless of histology.

Chemotherapy should be considered for patients who have a good performance status with regimens based on platinum/fluoropyrimidine combinations. Epirubicin, cisplatin, and infusional 5-FU (ECF) or ECX, where intravenous 5-FU is replaced by oral capecitabine are current standards of care in Princess Margaret Cancer Centre (Cunningham et al., 2006, 2008).

Adenocarcinomas of the esophagogastric junction should be screened for Human epidermal growth factor receptor 2 (Her-2) protein overexpression or gene amplification. In patients with Her-2 positive metastatic tumours, palliative chemotherapy should include trastuzumab in addition to a cisplatin/fluoropyrimidine combination (Bang et al., 2010).

The use of cetuximab, panitumumab and bevacizumab in combination with chemotherapy is being explored in clinical trials but remains experimental. REAL3 examined the addition of panitumumab to modified epirubicin, oxaliplatin, capecitabine (EOX) (reduction in oxaliplatin to 100 mg/m² and capecitabine to 1000 mg/m² per day) in esophagogastric cancer was associated with a similar response rate but a significantly worse overall survival (median 8.8 versus 11.3 months) (Waddell Lancet Oncol 2013). Currently these combinations can not be recommended outside of trials.

5.2.3 Treatment of metastatic disease – second-line chemotherapy
There is no standard approach for second-line therapy. For patients who retain an adequate 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 example, patients who received epirubicin, cisplatin, 5-FU (ECF) or EOX initially could be offered single agent irinotecan, a taxane or irinotecan plus 5-FU/leucovorin (FOLFIRI). A multicentre, randomized phase III trial comparing second line chemotherapy (either docetaxel 60 mg/m² every 3 weeks or irinotecan 150 mg/m² every 2 weeks) plus best supportive care for pretreated advanced gastric cancer significantly improved overall survival when added to best supportive care (Park et al., 2011). Similarly, a phase III trial of second line docetaxel in patients with relapsed esophagogastric adenocarcinoma who progressed within 6 months of previous platinum/fluoropyrimidine demonstrated a median overall survival of 5.2 months versus 3.6 months among those who received active symptom control (Ford et al., 2013). Paclitaxel may also be given as second line therapy. Consideration should otherwise be given to inclusion in clinical trials.

5.2.4 Radiotherapy
Palliative radiotherapy is an effective modality for the relief of dysphagia, other mass effect (eg. airway compression) and bleeding. Brachytherapy provides more durable dysphagia relief than stent and should be considered for patients with longer life expectancy. The choice between external beam and brachytherapy is generally based on whether the disease is causing esophageal lumen compromise alone, threatening other mediastinal structures, risk of bleeding as well as technical considerations. In patients with a short life expectancy (e.g. <2 months), stents provide rapid relief and is the preferred first option.

External beam radiotherapy alone (e.g. 20 Gy in 5 fractions or 30 Gy in 10 fractions) or brachytherapy (e.g. 10 Gy in 1 fraction or 12 Gy in 2 fractions) may be considered for palliative treatment of esophageal carcinoma, depending on the clinical situation, for relief of dysphagia, with metal stent placement being another option.

5.3 Oncology Nursing
Refer to general oncology nursing practices

6. Supportive Care

6.1 Patient Education
Refer to general patient education practices

6.2 Psychosocial Care
Refer to general psychosocial oncology care guidelines

6.3 Symptom Management
Refer to general symptom management care guidelines
6.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

6.5 Palliative Care

The goal of antineoplastic therapy in patients with advanced esophageal cancer is to palliate symptoms, including dysphagia and improve survival. Quality of life and minimization of side effects are key considerations when choosing chemotherapy regimen: multi-agent versus single agent in the advanced setting and radiotherapy dose fractionation.

7. Follow-up care

There are no randomized trials to guide the postoperative surveillance strategy, and no data that demonstrate improvement in quality of life or longevity from earlier detection of asymptomatic recurrences.

It is recommended to perform history, physical examination, and targeted blood work every three to four months for the first two years, four to six monthly year three to four, six to twelve monthly on year five. CT scans of the chest and abdomen may be done at the discretion of the treating physicians.

Surveillance endoscopy may be carried out if there was a preoperative history of Barrett’s esophagus, a questionable margin at the time of surgery, or if the patient has a recalcitrant stricture that is worrisome for an occult local recurrence. Surveillance endoscopy is recommended for patients treated with chemoradiation alone who may be surgical candidates if they fail in the esophagus alone without distant progression.

For patients with advanced disease receiving active treatment, response is routinely evaluated with CT scans at the discretion of the treating physician every 2-3 months. Endoscopy is only recommended if clinically indicated.
8. References


