PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GASTROINTESTINAL

ESOPHAGEAL CANCER
GI Site Group – Esophageal cancer

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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. Important changes in the staging system in the 7th edition primarily relate to changes in nodal staging: N1: 1-2 nodes, N2: 3-5 nodes, N3: > 6 nodes, celiac nodes are no longer considered M1a disease for tumours of the distal esophagus or gastroesophageal junction. Furthermore, the esophageal staging has been harmonized with gastric staging.

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).

Surgery alone can 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.

Surgery alone is not a standard treatment for locally advanced disease (T3-4 N0-1 M0 or T1-4 N0-1 M1 or with N2/N3 nodal involvement).

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 (Omlooo 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. Recently it has been recognized that 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 stage I 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. Options include cisplatin 100 mg/m$^2$ plus 5-FU 1000 mg/m$^2$/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) or the low dose weekly carboplatin (area under the curve of concentration X time [AUC] 2) plus weekly paclitaxel 50 mg/m$^2$ plus concurrent radiotherapy (41.4 Gy over five weeks) regimen as was used in the Dutch CROSS trial (van Hagen et al., 2012). 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 and is likely to become the favoured regimen. The role of newer chemotherapy drugs combined with radiotherapy is being investigated.

The policy in Princess Margaret Cancer Centre at this time for preoperative chemoradiotherapy is cisplatin 25 mg/m$^2$ IV day 1-4 and 5-FU 1000 mg/m$^2$/24 hours via continuous infusion day 1-4 on week 1 and 5 in conjunction with radiotherapy 50 Gy in 25 Fr over 5 weeks. With new provincial guidelines from the Program of Evidence Based Medicine now supporting the CROSS trial regimen with carboplatin/paclitaxel and concurrent radiotherapy the policy will likely shift within this year (2013) once drug funding is available.

The benefit of preoperative chemoradiotherapy for patients with T1N0 esophageal or esophagogastric junction adenocarcinoma or squamous cell carcinoma is less clear. Surgery alone can be recommended in these patients.

Definitive chemoradiotherapy is a reasonable approach for patients who are not surgical candidates or in patients who do not wish to undergo surgical resection (Herskovic et al., 1992). In this study, patients received two cycles of infusional 5-FU (1000 mg/m$^2$ per day, days 1 to 4, weeks 1 and 5) plus cisplatin (75 mg/m$^2$ 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. Radiotherapy alone can be considered in patients with a performance status which may preclude systemic therapy.

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 treatment

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. In a preliminary report of the REAL3 trial presented at ASCO 2012, 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). Currently these combinations can not be recommended outside of trials.

5.2.3 Treatment of metastatic disease – second-line treatment
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/m\(^2\) every 3 weeks or irinotecan 150 mg/m\(^2\) 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.

5.3 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 chemotherapy 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 a chemotherapy regimen: multi-agent versus single agent in the advanced setting.
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.

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


