Oesophageal Cancer

Epidemiology\[1\]

Carcinoma of the oesophagus is a common, aggressive tumour. Several histological types are seen, almost all of which are epithelial in origin. The vast majority of these tumours will be either squamous cell carcinoma (SCC) or adenocarcinoma (AC).

Over a period of two decades the incidence of SCC has remained relatively stable or declined (particularly associated with smoking and alcohol), whilst there has been a rapid rise in the amount of AC seen, particularly in Caucasian males.\[2, 3\] This has now overtaken SCC as the most common form of oesophageal tumour in some developed countries. One study, however, suggests that the incidence of AC in America may have reached a plateau.\[4\]

The majority of cases (80-85%) are diagnosed in less developed countries; most of these are SCC.

Incidence rates in the UK are considerably higher than the EU average.

Incidence\[1\]

- Carcinoma of the oesophagus represents the 13th most common malignant tumour in the UK, and is the 8th most common cancer in the world.
- There were 8,332 people diagnosed with oesophageal cancer in the UK in 2011, with approximately twice as many cases occurring in men as in women. This equates to an annual incidence of 18.0 per 100,000 in men and 8.5 per 100,000 in women. The male:female ratio for the adenocarcinoma subgroup is 52:10.
- The number of new cases of AC in the UK is approximately 6.4 per 100,000.
- In the UK between 2009 and 2011, an average of 42% of cases were diagnosed in people aged 75 years and over, with more than eight out of ten (83%) occurring in those aged 60 and over.

The incidence of oesophageal carcinoma varies considerably with geographical location, with high rates in China and Iran, where it has been directly linked to the preservation of food using nitrosamines. AC is seen more frequently in Caucasian populations, whereas SCC is more frequent in people of African descent.\[5\] There is considerable geographical variation of lower oesophageal cancer within the UK, the reason for which is being investigated.\[6\]

Risk factors\[7, 8\]

- The use of tobacco and alcohol are strong risk factors for both SCC and AC and have a synergistic effect in this respect for SCC and additive effect for AC. Cigarette smoking is associated with a 10-fold increase in risk for SCC and a 2- to 3-fold increase in risk for AC.\[9\] The relative increase in risk caused by smoking remains high for AC, even after 30 years of giving up smoking, but reduces within 10 years for SCC.\[10\]
- Barrett's oesophagus, which is a precursor of AC.
- Chronic inflammation and stasis from any cause increase the risk of oesophageal SCC - eg, strictures due to caustic injury or achalasia.
- Tylosis and Paterson-Brown-Kelly syndrome are also associated with an increased risk for SCC.
- Obesity has been linked with increased risk for AC but reduced risk for SCC. Obesity increases the risk of gastro-oesophageal reflux disease (GORD), in turn increasing the risk of Barrett's oesophagus. The relationship between obesity and the rise in AC has, however, been questioned. A review of the Connecticut Tumor Registry data between 1940-2007 showed that the increase in AC seen in the 1960s predated the rise in obesity by a decade.\[11\] The authors of the review propounded that this may have been linked to a decrease in the incidence of Helicobacter pylori infection or environmental factors.
- One Japanese study showed a link between oesophageal cancer and tooth loss.
- A family history of hiatal hernia is a risk factor for oesophageal adenocarcinoma, and some people appear to have a genetic predisposition to developing types of gastro-oesophageal cancers.\[12\]

Presentation

The classic RED FLAG symptoms are:

- Dysphagia.
- Vomiting.
- Anorexia and weight loss.
- Symptoms of gastrointestinal-related blood loss.
Oesophageal cancers often present late in the progress of the disease, because approximately 75% of the circumference of the oesophagus must be involved before symptoms of ‘food sticking’ are experienced. As a result, approximately half of the patients who present as a result of developing symptoms, will already have an unresectable tumour or distant metastases.

Symptoms and signs of oesophageal cancer which may cause a patient to present to a doctor include:

- Dysphagia
- Weight loss
- Loss of appetite
- Odynophagia
- Hoarseness
- Melaena
- Retrosternal pain
- Intractable hiccups
- Lymphadenopathy

Differential diagnosis

These include:

- Oesophageal stricture from any cause.
- Compression of the oesophagus from external sources - eg, enlarged lymph glands or bronchial carcinoma.
- Achalasia.
- Gastric cancer.
- Intramural benign tumours - eg, leiomyoma.
- Metastatic tumours - most commonly from breast.

Investigations

The initial investigation of a patient with symptoms suggestive of oesophageal carcinoma should include:

- FBC, U&E, LFT, glucose, CRP.
- Urgent endoscopy - with brushings and biopsy of any lesion seen.

Other possible staging investigations include:

- CXR - looking for evidence of metastases.
- Double-contrast barium swallow.
- CT/MRI scan of the chest and upper abdomen - for staging purposes.
- Fluorodeoxyglucose positron emission tomography (FDG-PET) scan - for accuracy of staging (combined with CT).

Less commonly:

- Endoscopic ultrasound - increases accuracy of staging.
- Fine-needle aspiration - of any palpable cervical lymph node; ±
- Bronchoscopy - in high oesophageal tumours or if hoarseness or haemoptysis is present.

Chromoendoscopy (use of dyes), high-resolution endoscopy, spectroscopy, narrow band imaging (optical filter technology that improves the visibility of blood vessels) and autofluorescence (exploits the natural emission of light by biological tissues) are other modalities being investigated.

Editor’s Note

Dr Hayley Willacy draws your attention to the recently released NICE guidance on the assessment and management of oesophago-gastric cancer[^13]. The guideline covers not only staging and managing oesophageo-gastric cancer but also includes radical and palliative treatment options and advice about nutritional support. It aims to improve organisation of care and support, and improve quality of life and survival by giving advice on the most suitable treatments depending on cancer type, stage and location.

Staging[^14]
<table>
<thead>
<tr>
<th>T category</th>
<th>Depth of infiltration</th>
<th>N category</th>
<th>Regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>NX</td>
<td>Nodes cannot be assessed</td>
</tr>
<tr>
<td>T1</td>
<td>Invasion of lamina propria/submucosa</td>
<td>N0</td>
<td>No node spread</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion of muscularis propria</td>
<td>N1</td>
<td>Regional node metastases</td>
</tr>
<tr>
<td>T3</td>
<td>Invasion of adventitia</td>
<td>M0</td>
<td>No distant spread</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion of adjacent structures</td>
<td>M1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Management**\(^{15, 16}\)

Primary treatment modalities include surgery alone or with chemotherapy or radiation therapy.\(^{[3]}\) Options should be selected after discussion with the patient, following a multidisciplinary meeting to consider staging, nutritional status and comorbidities.

**Surgery**

- Antibiotic and antithrombotic prophylaxis should be instituted.
- Endoscopic mucosal resection and submucosal dissection is an option for patients with early oesophageal cancer.\(^{[17]}\)
- Endoscopy is frequently combined with other modalities - for example, photodynamic therapy (PDT).\(^{[18, 19]}\) A photosensitising agent is injected and then activated by exposing the tumour to light, usually a low-power laser, via an endoscope. The agent absorbs energy from the light and produces high-energy oxygen molecules that destroy tumour cells. This is an outpatient procedure, under sedation. In one series, five-year disease-specific survival was 76% in 56 treated with PDT as monotherapy.\(^{[20]}\)
- Other techniques employed with endoscopy to treat early cancers include lasers, electrocoagulation, argon plasma coagulation (APC) and radiofrequency ablation.
- Endoscopic resection can also be used for more advanced tumours when the patient is unwilling or unfit to undergo more invasive surgery.\(^{[20]}\)
- Oesophagectomy is the treatment of choice for most advanced cancers. The approach may be either through the diaphragm (transhiatal) or transthoracic and there is no clear evidence to support one method over the other.
- Minimally-invasive (endoscopic) oesophagectomy is recommended by the National Institute for Health and Care Excellence (NICE), provided it is performed by experienced surgeons and the patient is entered into the National Oesophago-Gastric Cancer Audit.\(^{[21]}\)
- Abdominal lymphadenectomy is beneficial in both SCC and AC. Mediastinal lymphadenectomy is of benefit in SCC but in AC the evidence base is less supportive.
- Chemoradiotherapy is recommended for localised SCC of the proximal oesophagus. More distally, surgery may also be required.
- Pre-operative chemoradiotherapy is recommended for AC. Pre-operative radiotherapy alone is of no benefit but chemotherapy before surgery improves survival.

**Palliation**\(^{[15, 22]}\)

Many patients will present late in the disease process with unresectable disease. For this group of patients, the emphasis will be on palliation and symptom relief.

- Radiotherapy, brachytherapy, chemotherapy, electrocautery or plasma/laser ablation may be of use (primarily in reducing tumour bulk and bleeding). Photodynamic therapy may also be used for palliation in advanced disease.\(^{[19]}\)
- Trastuzumab in combination with cisplatin/fluoropyrimidine should be considered for patients with HER2-positive oesophagogastric junctional AC.\(^{[23]}\)
- Stenting is a first-line option to assist swallowing.
- Nutritional status may be maintained by the use of liquid feeds, enteral nutrition or percutaneous endoscopic gastrostomy (PEG) tubes.
- Pain relief should be maintained at a level at which the patient experiences little, or no pain.

**Prognosis**\(^{[24]}\)

The patient’s pre-operative status, comorbidity and presence or absence of metastases are strong predictors of outcome. The prognosis for oesophageal carcinoma varies depending on the stage at presentation. The overall five-year survival rate is 20-25% for all stages. Not surprisingly, lymph node involvement equates with a poorer prognosis. The survival rate for AC and SCC are the same.

A study of 1,085 patients who underwent oesophagectomy showed a 4% operative mortality rate and a 23% survival rate. For patients who had pre-operative chemoradiotherapy, the prognosis improved to 48%.

**Prevention**\(^{[15]}\)

Reducing risk factors (obesity, smoking and alcohol) should help.
Earlier detection through screening and surveillance will improve survival rates. However, standard diagnostic tools (eg, endoscopy with biopsy) have several limitations as screening tools - including low negative predictive value and relatively high cost.

**Further reading & references**

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18. Photodynamic therapy for early oesophageal cancer; NICE Interventional Procedure Guidance, December 2006
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