

Oesophageal cancer: current trends and management

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ABSTRACT The incidence of oesophageal cancer continues to increase worldwide, particularly adenocarcinoma of the distal oesophagus and gastro-oesophageal junction. Unfortunately, overall survival rates remain disappointingly low, even in those patients who are fit for radical (curative) treatment at presentation. Surgery, with or without preoperative chemotherapy, remains the treatment of choice in the UK for those patients of adequate performance status who have potentially resectable disease. An alternative approach is chemoradiotherapy, which is associated with similar long-term survival rates, at least in patients with squamous cell carcinoma. The survival of patients with advanced disease may be prolonged by palliative chemotherapy, and there are a number of treatment modalities that may be used to relieve dysphagia; their use often reflects local availability and expertise. This review summarises the recent trends in the incidence and aetiology of oesophageal cancer and provides an up-to-date overview of its management.

KEYWORDS Adenocarcinoma, chemoradiotherapy, multidisciplinary (care or team), oesophagectomy

DECLARATION OF INTERESTS No conflict of interests declared.

INTRODUCTION

Oesophageal cancer is the eighth most common cancer worldwide, with an estimated 462,000 new cases in 2002. In the UK in 2004, 7,654 people were diagnosed with oesophageal cancer, which is responsible for around 5% of all cancer deaths.

PATHOLOGY AND AETIOLOGY

Two main types of malignant tumours arise in the oesophagus: squamous carcinomas, the majority of which arise in the upper two-thirds of the oesophagus, and adenocarcinomas, most of which originate in the lower third or bridging the gastro-oesophageal junction. Other much rarer histological subtypes such as lymphoma, gastrointestinal stromal tumour and small cell carcinoma will not be covered in this review. Squamous carcinoma is strongly associated with tobacco and alcohol consumption and has been stable or declining in incidence over recent years. In contrast, oesophageal adenocarcinoma is the most rapidly increasing cancer in many Western countries and has now become the dominant histological tumour type in the US and Western Europe. Adenocarcinoma is associated with gastro-oesophageal reflux disease (GORD) and Barrett's oesophagus (where the native squamous epithelium is replaced by abnormal glandular epithelium), as well as with obesity.

Owing to a rich network of submucosal lymphovascular channels, oesophageal tumours can spread some distance longitudinally away from the primary mucosal location,

causing so-called 'skip lesions'. Lymphatic spread to para-oesophageal and mediastinal lymph nodes occurs early on and is usual by the time of clinical presentation. Haematogenous spread is more common with adenocarcinomas, the most frequent sites being the liver, lungs, bone and brain. In the case of squamous cancer, the aetiological carcinogenic factors may cause a 'field change' in the mucosa of the aerodigestive tract, leading to an increased risk of second malignancy after successful treatment of the initial tumour.

PRESENTING FEATURES OF DISEASE

The most common presenting symptom of oesophageal cancer is difficulty swallowing (dysphagia), which is graded according to the patient's ability to swallow, as follows:

- Grade 1: able to swallow most foods
- Grade 2: soft foods only
- Grade 3: liquids only
- Grade 4: unable to swallow anything

The National Institute for Health and Clinical Excellence's (NICE) 2001 Improving Outcomes Guidance (IOG) recommends that patients with dysphagia of any age should be referred urgently to the upper gastrointestinal diagnostic team for investigation within two weeks of presentation. However, significant dysphagia often represents advanced disease. Other symptoms of oesophageal cancer include pain on swallowing (odynophagia) and weight loss. Physical signs may be minimal at presentation apart from weight loss. Patients with metastatic disease may have palpable supraclavicular lymphadenopathy or hepatomegaly.

Published online February 2008

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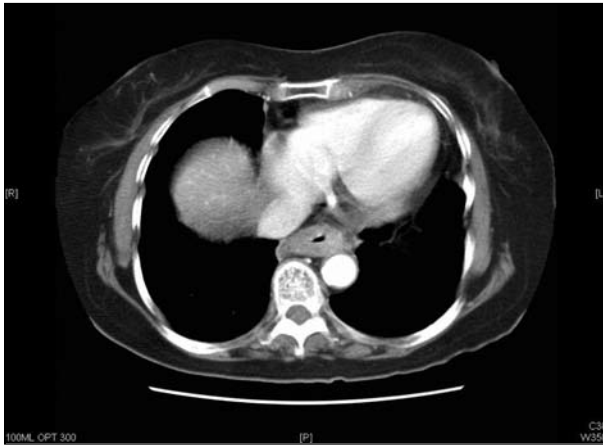


FIGURE 1 Axial CT scan showing a T3N1 adenocarcinoma of the oesophagus.

INVESTIGATIONS AND STAGING

The diagnosis of oesophageal cancer is usually made by endoscopy and biopsy. Staging investigations include a computerised tomography (CT) scan of the thorax and abdomen (see Figure 1). Patients suitable for potentially curative treatment should also have an endoscopic ultrasound scan (EUS), and a laparoscopy may be considered if the tumour crosses the gastro-oesophageal junction. The role of positron emission tomography (PET) is not yet clear, though it may prevent unnecessary surgery, thus making it cost effective.

Oesophageal cancers are staged according to the tumour, node, metastasis (TNM) classification of malignant diseases as shown in Table 1.

MANAGEMENT

In the UK, the management of patients with oesophageal cancer requires multidisciplinary care by specialist teams practising within managed networks, with clear referral pathways between primary care and diagnostic units and between secondary and tertiary centres. Patients should have access to high quality information delivered in a format that is appropriate to their level of need, and access to upper GI clinical nurse specialists, dieticians and specialist palliative care services (see www.sign.ac.uk/pdf/sign87.pdf).

THERAPEUTIC OPTIONS FOR NON-METASTATIC DISEASE

Oesophageal cancer may be treated with surgery, radiotherapy, chemotherapy or a combination of all three, but cure rates remain disappointingly low. The overall five-year survival rate in patients suitable for radical treatment ranges from 10% to 40%. It is unclear whether any intervention or screening improves the outcome from invasive malignancy in patients with Barrett's oesophagus. Patients who have developed high-grade dysplasia should

TABLE 1 TNM staging of oesophageal cancer

Tumour stage	
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
Nodal stage	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis	
M0	No distant metastasis
M1a	Metastasis in cervical lymph nodes (upper thoracic oesophagus) or coeliac lymph nodes (lower thoracic oesophagus)
M1b	Other distant metastasis

be considered for photodynamic therapy, endoscopic mucosal resection, laser therapy or argon plasma coagulation; surgical resection may be considered for patients with widespread high-grade dysplasia occurring in a long segment Barrett's oesophagus.

SURGERY

Surgical resection has been the cornerstone of curative therapy for oesophageal cancer and should be considered for all patients with potentially resectable disease (T1–3, N0–1) who have no evidence of metastatic disease (M0) and are medically fit for surgery. Resection rates vary from 25% to 50% in different countries, but appear to be falling in the UK as a result of better patient selection and staging. A transthoracic (Ivor Lewis) oesophagectomy involves abdominal mobilisation of the stomach and transthoracic resection of the oesophagus. In contrast, transhiatal oesophagectomy involves abdominal resection of the oesophagus followed by anastomosis of the stomach to the cervical oesophagus. Proponents of the transthoracic approach claim it allows direct visualisation of the tumour and extended lymphadenectomy, but an improvement in survival has not been demonstrated. Transhiatal oesophagectomy appears to be associated with a lower incidence of pulmonary complications and is often preferred in patients with pre-existing chest disease and/or no obvious lymphadenopathy. Radical oesophagectomy, by either approach, is associated with a perioperative mortality rate of 5–10% and a perioperative morbidity rate of 30–40%. Minimally invasive techniques of oesophageal

resection are being developed in an attempt to reduce the morbidity and mortality of surgery.

The overall two- and five-year survival rates after radical oesophagectomy are around 45% and 20%, respectively. The 2001 NICE/IOG guidelines (see further reading) recommend that radical oesophagectomy should only be carried out by designated surgeons within specialist multidisciplinary teams serving a population of 1–1.5 million. The reconfiguration of services necessary for this to be achieved in practice has not yet been successfully implemented in some parts of the UK.

Preoperative (neoadjuvant) chemotherapy

In the UK, most patients undergoing radical oesophagectomy for locally advanced (T3/4 N1) disease will be offered neoadjuvant chemotherapy, based on the results of a multicentre study conducted by the Medical Research Council (MRC OEO2) that showed a 9% improvement in two-year survival in patients who were given two cycles of cisplatin and 5-fluorouracil (5-FU) chemotherapy (over six weeks) prior to surgery, compared with those who were not. Currently, another UK MRC trial (OEO5) is investigating whether four cycles of 'optimum' chemotherapy with ECX (epirubicin, cisplatin and capecitabine) is better than standard therapy.

Preoperative chemoradiotherapy

Combining chemoradiotherapy (CRT) and surgery attempts to use the benefits of all three single-treatment modalities. Results from randomised trials comparing preoperative CRT to surgery alone are conflicting, but patients who achieve a pathological complete response (no residual tumour in the surgical specimen) after CRT have an improved outcome. It is not clear whether these patients benefit from the addition of surgery, but there is currently no reliable test to select the 25–30% of patients who achieve this outcome. Combined modality treatment is associated with increased morbidity and a higher postoperative mortality rate, and is not currently recommended as standard practice.

DEFINITIVE (RADICAL) CHEMORADIOOTHERAPY

Most patients with oesophageal cancer are not suitable for (and some may not want) radical resection. Furthermore, patients who die within two years of surgery never regain their preoperative quality of life. Therefore, patients have to be rigorously selected for surgery, and non-surgical management will be more appropriate for a significant proportion of patients.

Radiotherapy alone rarely cures oesophageal cancer. However, a pivotal study (US Intergroup RTOG 85-01), which mainly included patients with squamous cell oesophageal carcinoma, showed that radical CRT is significantly more effective than single modality therapy

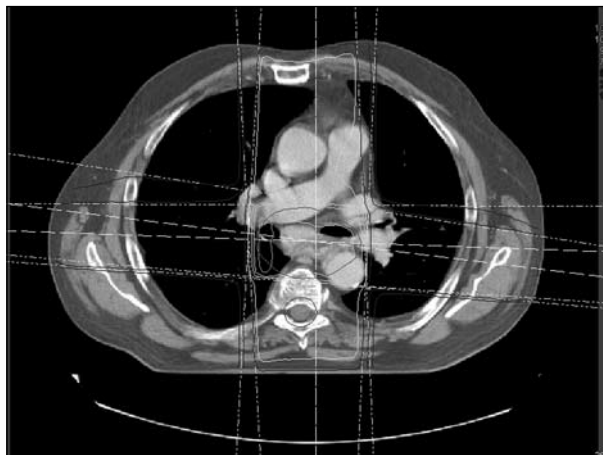


FIGURE 2 Radiotherapy plan for treatment of an oesophageal carcinoma. The oesophageal tumour (inner white circle) with a margin (outer black circle) is treated to the prescribed dose using four radiotherapy beams.

and is associated with a five-year survival rate of 27%. Similar survival rates with CRT have been found in other series, for example in 90 cases of inoperable oesophageal cancer treated in the UK; two- and five-year survival rates were 51% and 26%, respectively. As expected, combined modality therapy is associated with greater toxicity, with around 50% of patients experiencing moderate to severe mucosal and haematological side effects. In many centres CRT is being offered as an alternative to surgical resection for patients with squamous cell carcinoma.

What does radiotherapy involve?

Radical external beam radiotherapy for oesophageal cancer requires complex three-dimensional conformal planning. The oncologist will outline the target volume for treatment on a CT scan, aiming to treat the gross disease (primary oesophageal tumour and involved lymph nodes as demonstrated on EUS and/or PET). A margin is then applied to allow for subclinical microscopic disease and for day-to-day variations in patient positioning and treatment set-up. Once the target volume has been defined, the treatment planning team will determine how to arrange 4–5 radiotherapy beams to provide optimum coverage of the target volume while keeping the dose to critical structures, including the spinal cord, heart and lungs, within safe limits. Radiotherapy is usually given in 20–30 fractions (or doses) over 4–6 weeks delivering 45–54 Gy to the target volume. An example of a radiotherapy plan for treatment of oesophageal carcinoma is shown in Figure 2.

What does chemotherapy involve?

The most common chemotherapeutic agents used concurrently with radiotherapy are cisplatin and 5-FU. Both have good single-agent activity in oesophageal cancer and are among the best radiosensitisers in tumour models. 5-FU has traditionally been given as a continuous infusion throughout CRT via a central venous line. Capecitabine is an oral 5-FU pro-drug that can be used

instead of 5-FU; after absorption it is converted to 5-FU via enzymes in the liver and tumour tissue.

A further six weeks of chemotherapy may be given as a neoadjuvant (induction) phase, and this often improves the patient's dysphagia prior to starting radiotherapy. Common side effects of cisplatin and capecitabine chemotherapy are nausea, bone marrow suppression (neutropenia, thrombocytopenia), mucositis (mouth ulcers, stomatitis, diarrhoea) and palmar-plantar erythema (redness and cracking of the skin on the palms and soles).

Targeted agents with CRT

Most patients who relapse after CRT do so within the previously irradiated area. Tumour cell repopulation during radiotherapy is one mechanism that can lead to radio-resistance, and repopulation may occur because of activation of the epidermal growth factor receptor (EGFR) by radiotherapy. A monoclonal antibody (cetuximab) that specifically blocks the EGFR has shown promise in combination with radiotherapy in other tumour types and is currently being tested in a UK trial (SCOPE-1) in combination with CRT in patients with oesophageal cancer.

MANAGEMENT OF LATE-STAGE DISEASE

At presentation, 60% of oesophageal cancer patients cannot be treated radically either because their tumours are too advanced or their performance status is too poor. Palliative treatment options include:

1. Endoscopic expandable metallic stent insertion, which produces rapid though incomplete relief of dysphagia in most patients but may be associated with pain;
2. Laser-thermal Nd-YAG endoluminal tumour destruction and photodynamic therapy, which require repeated treatments and may be better for short exophytic tumours;
3. Radiotherapy, either as short-course (2–3 weeks) external beam radiotherapy or single-dose intraluminal brachytherapy (placing a radioactive source close to the tumour), which is best for

patients with minimal dysphagia because the benefits are not evident for at least a month;

4. Chemotherapy: ECF/X (epirubicin, cisplatin and 5-FU or capecitabine) is the combination most frequently used. Chemotherapy improves median survival from 5 to 11 months but may be associated with significant toxicity.

Treatment choices have to be tailored to each individual patient and may in part be dependent on local availability and expertise in the use of these palliative procedures.

CONCLUSION

The overall five-year survival rate for patients with oesophageal cancer remains less than 10%. To improve this figure, it is clear that public health measures are required to reduce the incidence of disease and diagnose patients at an earlier stage. In the meantime, efforts must continue to improve locoregional and systemic therapies, and services should be configured so that patients have equitable access to the highest quality of care.

KEY POINTS

- Oesophageal cancer is increasing in incidence, particularly adenocarcinoma of the distal oesophagus associated with gastro-oesophageal reflux disease (GORD).
- Patients who have resectable disease and are fit for surgery should undergo radical oesophagectomy with or without neoadjuvant chemotherapy.
- Preoperative chemoradiotherapy remains investigational, but definitive chemoradiotherapy is associated with long-term survival in suitable patients.
- Up to 60% of patients cannot have radical treatment because of tumour or patient factors, and palliative treatment for these patients must be tailored to their individual needs.
- Improving the overall survival from oesophageal cancer depends on earlier detection as well as advances in treatment.

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Originally published as part of the Oncology module in the RCPE Online Continuing Medical Education Programme. Online CME, including self-assessment MCQs, is available to Fellows and Members at: <http://www.rcpe.ac.uk>