

Diagnosis and management of oesophageal cancer

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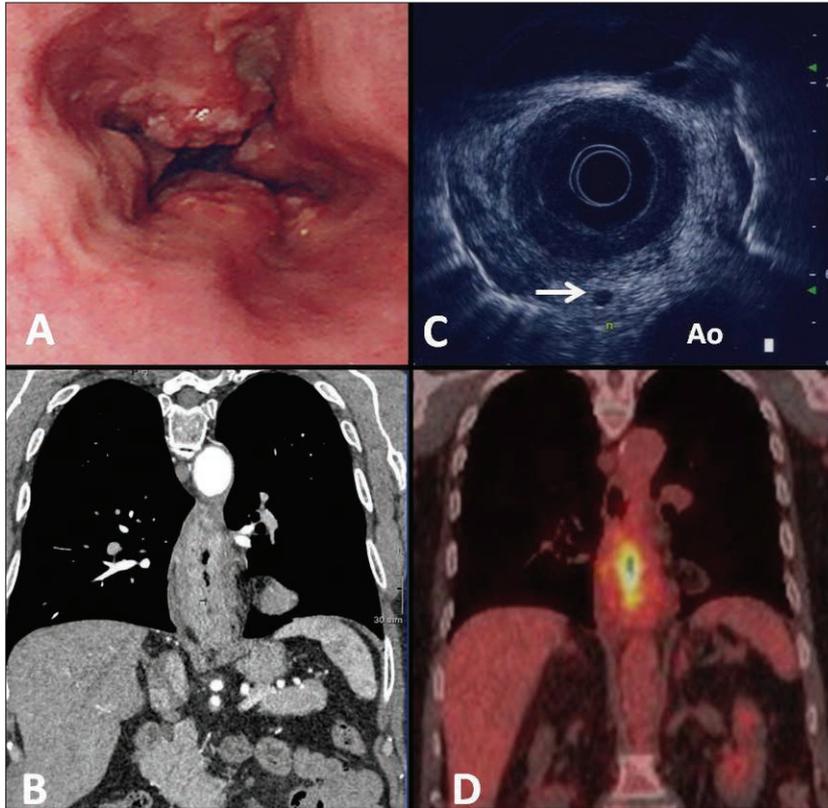


FIGURE 1
 Diagnosis and staging of oesophageal cancer: **A** Urgent endoscopy for dysphagia allows biopsy of a stricture in the lower oesophagus confirming adenocarcinoma **B** Initial whole body computerised tomography staging showing stricture but no other lesion **C** Endoscopic ultrasound showing a thick oesophageal wall (black ring) but no contact with the aorta (Ao); however a small adjacent lymph node (arrowed) is seen likely to contain cancer which is too small to see on the PET CT scan (**D**) which shows the tumour as 'hot' but no other liver or lymph node metastases

What are the common presenting symptoms?

How should diagnosis be confirmed?

What are the treatment options?



OESOPHAGEAL CANCER RATES ARE CONTINUING TO INCREASE WITH 7,500 NEW CASES DIAGNOSED

in the UK in 2016 compared with 7,000 in 2013. Oesophageal cancer is the thirteenth most common cancer in the UK,¹ however, its outcome remains poor making it the fifth most common cause of cancer deaths.²

Early diagnosis improves survival rates. Both the National Institute for Health and Care Excellence (NICE)³ and European Society of Medical Oncology (ESMO)⁴ have published updated guidance which aims to improve outcomes in this potentially curable cancer.

The two main types of oesophageal cancer, oesophageal squamous cell

carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), have different pathogenesis but similar presentation. Both carry a very poor five-year survival of 17% compared with the more common cancers such as colorectal (60%), prostate (88%) and breast cancer (86%).²

The UK has the highest incidence of OAC in Europe in females and the second highest in males.⁵ OAC is the more common form of oesophageal cancer seen in the UK and other developed countries, whereas OSCC remains more common globally.⁶

Oesophageal cancer is twice as common in men than women and the vast majority of patients are over the age of 50 at presentation with peak

incidence in the 65-75 age group.⁵

Risk factors for oesophageal cancer are listed in box 1, p22

PRESENTATION

Patients commonly present with dysphagia or odynophagia which may be accompanied by weight loss and vomiting. Although a variety of other conditions may cause dysphagia, see table 1, p22, referral for urgent endoscopy should always be considered in the presence of dysphagia regardless of previous history or medication. Dysphagia, weight loss and age are strong positive predictors for cancer. In a study on symptom referral for rapid access endoscopy, 92% of patients with

SPECIAL REPORT

OESOPHAGEAL CANCER

malignancy had either dysphagia, weight loss or were over the age of 55 with other alarm symptoms.¹⁴ Because of its importance as a predictor for cancer, any subjective history of weight

loss in the absence of any known illness should be considered.^{15,16}

Advanced tumours can present without dysphagic symptoms due to the elastic nature of the oesophagus.

Patients with advanced disease may present with anaemia and haematemesis, resulting from bleeding lesions, hoarse voice caused by early mediastinal invasion or weight loss which may indicate metastatic spread.

At risk or alarm symptoms for oesophago-gastric cancer that should prompt endoscopy referral have been highlighted in the NICE guidelines for referral for suspected cancer¹⁷ and ESMO⁴ guidelines and also previously published guidelines by the British surgical and gastroenterological societies.¹⁸

Box 1

Risk factors for oesophageal cancer

- **Smoking⁶**

Smoking is a major risk factor for both types of oesophageal cancer and is linked to an estimated two-thirds of cases in the UK.³

- **Excess alcohol intake⁶**

- **Chewing betel leaf⁶**

- ***Gastro-oesophageal reflux disease (GORD)⁷**

- **Obesity (particularly central)⁸**

- **Barrett's oesophagus**

Barrett's oesophagus is a precursor and risk factor for OAC. The risk of developing OAC with Barrett's oesophagus is currently 0.1-0.47% per year.⁹⁻¹¹ Diagnosis of Barrett's oesophagus generally triggers endoscopic surveillance to enable early diagnosis in the event of cancer developing which improves survival.¹²

*The diagnosis and management of GORD has been discussed in a previous article in this journal¹³

Table 1

Causes of dysphagia⁵³

Intraluminal	Food impaction or damage
Extrinsic compression	Goitre Osteophyte Lymphadenopathy
Intrinsic causes	Oesophageal carcinoma Reflux-associated stricture or ulceration Bisphosphonate-induced stricture Doxycycline/tetracycline therapy Eosinophilic oesophagitis Oesophageal web Oesophageal candidiasis Schatzki ring
Motility disorders	Achalasia Oesophageal dysmotility Functional dysphagia Systemic sclerosis Sjögren's syndrome Oesophageal spasm
Neurological disorders	Stroke Parkinsonism Multiple sclerosis Motor neurone disease
Others	Post surgery Post radiation Polymyositis

'Dysphagia, weight loss and age are strong positive predictors for oesophageal cancer'

The NICE recommendations for endoscopy referral to assess for suspected upper gastrointestinal (GI) and oesophageal cancer are shown in table 2, opposite.¹⁷ The recommendations from NICE differ slightly from those in other earlier guidelines regarding who to refer urgently or to consider for non-urgent endoscopy. The British surgical and gastroenterological societies recommend rapid access endoscopy for all patients over 55 with recent onset dyspepsia regardless of a response to treatment or all patients with alarm symptoms irrespective of age.¹⁸ Guidance from ESMO is similar to that from NICE and recommends an upper GI endoscopy for all patients with new dysphagia, GI bleeding, recurrent aspiration or nausea, weight loss and/or loss of appetite.⁴

As the NICE guidance is the most recent it should probably be used as initial guidance for the urgency of referral for direct endoscopy. However, patients over 55 with dyspepsia should be thoroughly reviewed to assess for a complete response to treatment. Non-urgent referral for endoscopy is advisable when there is any clinical suspicion, persisting unexplained upper GI symptoms, or proton pump inhibitor (PPI) treatment is required long term (> 6 weeks).

DIAGNOSIS

Patients with dysphagia should undergo upper GI endoscopy with biopsy to confirm a diagnosis of oesophageal cancer. Lesional biopsy

Table 2**NICE guidance on referral for suspected oesophageal cancer¹⁷****Urgent direct access (within 2 weeks) for upper gastrointestinal endoscopy**

- Dysphagia
- Aged 55 or over with weight loss and any of the following:
 - Upper abdominal pain
 - Reflux
 - Dyspepsia

Consider non-urgent direct access for upper gastrointestinal endoscopy for:

- Episode of haematemesis
- Aged 55 or over with:
 - Treatment-resistant dyspepsia
 - Upper abdominal pain with low haemoglobin levels
 - Raised platelet count with any of the following:
 - nausea, vomiting, weight loss, reflux, dyspepsia, upper abdominal pain or
 - Nausea or vomiting with any of the following:
 - weight loss, reflux, dyspepsia, upper abdominal pain

with histological interpretation is used to identify the cancer subtype and to exclude other potential causes such as severe GORD and ulceration, see table 1, opposite. If histology is benign but endoscopic appearances were suspicious of cancer, gastroscopy should be repeated. In severe reflux, gastroscopy with biopsies is repeated after 6 weeks of anti-acid treatment to ensure healing and exclude underlying cancer or Barrett's oesophagus or earlier if symptoms are progressive on PPI. Failure to diagnose oesophageal and gastric cancer at initial endoscopy is consistently around 10%. Hence, patients with unexplained symptoms should be considered for a second gastroscopy.^{19, 20}

PPIs may mask endoscopic findings and alter the appearance of malignant ulcers. Initial gastroscopy should follow a break in PPI therapy, usually of two weeks although there is no evidence on the best timing. If the patient is unable or unwilling to tolerate gastroscopy barium studies can be carried out.²¹ This approach may detect a stricture or mucosal ulceration. However, it does not enable histological sampling to differentiate between malignant and benign ulceration so diagnosis could be delayed.

DISEASE STAGING

If gastroscopy reveals a lesion suspicious of oesophageal cancer, the patient is warned and referred to a specialist upper GI surgery unit. The staging process enables patients and their doctors to choose appropriate treatments and avoid unnecessary surgery in those with advanced or incurable disease, see figure 1, p21.

Oesophageal cancer staging employs the Tumour, Nodal, Metastases (TNM) classification system.²²

Computed tomography (CT) of the neck, chest, abdomen and pelvis (whole body) is carried out initially to detect incurable disease.^{3, 4} CT has a 90% sensitivity for detecting distant metastasis > 1 cm and 85-100% sensitivity for detecting significant local invasion into adjacent mediastinal organs.²³⁻²⁵ If the patient has no distant metastases or local invasion, a clinical assessment for suitability for curative treatment including surgery is carried out. This will often include a formal objective cardiorespiratory assessment including exercise tolerance²⁶ or complex cardiopulmonary exercise testing.²⁷

Patients being considered for radical, curative treatment undergo complete TNM staging. Positron emission tomography (PET-CT) using F-18 fluorodeoxyglucose is recommended in all patients to detect distant lymph node or metastatic disease.³ Around 5-15% of patients with oesophageal cancer who are initially thought to be suitable for surgery are precluded from oesophagectomy after PET-CT staging.²⁸ Endoscopic ultrasound (EUS) can provide further assessment of, and possible tumour invasion into, nearby organs (such as the aorta) and sample suspicious lymph nodes but given its limited effect on management it is now only recommended in specific patients.^{3, 29}

Staging laparoscopy is indicated where the tumour involves the lower oesophagus and upper stomach and CT demonstrates potentially operable disease. Laparoscopy is able to detect

peritoneal and metastatic disease < 5 mm in diameter, and enables peritoneal cytology and biopsies to be obtained from suspicious lesions. Staging laparoscopy alters initial treatment decisions for invasive surgery in up to 28% of patients with gastric cancer following CT.³⁰ The stage of a cancer is closely related to prognosis emphasising the importance of early diagnosis.³¹

There is a high rate of synchronous second squamous lung and throat cancer in patients with OSCC due to chronic smoking and alcohol consumption therefore there is a low threshold for bronchoscopy and ear, nose and throat specialist review to exclude synchronous second cancer.²⁰

‘There is a high rate of synchronous second squamous lung and throat cancer in patients with oesophageal squamous cell carcinoma’

Patients should be supported by cancer nurse specialists and specialist dietitians during the staging process. The complex staging process is key to decision-making regarding suitability for curative surgery and treatment. If surgery is performed unnecessarily in patients with advanced disease the recovery from surgery may have a significant impact on the patient's quality of life for their remaining life expectancy.

MANAGEMENT

The specialist upper GI multidisciplinary team (MDT) involves consultant surgeons, radiologists, pathologists, oncologists, gastroenterologists, palliative care physicians as well as cancer nurse specialists and specialist dietitians. The patients' investigation results are considered alongside their fitness for surgery and/or chemotherapy at the MDT meeting. The final decision should be made together with the patient after the recommended treatment options have been carefully explained. Tumours that show local invasion (T4) or distant metastases (M1) are not amenable to curative treatment.



key points

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Oesophageal cancer rates are continuing to increase.

Oesophageal cancer is the thirteenth most common cancer in the UK, however, its outcome remains poor making it the fifth most common cause of cancer deaths. There are two main types; oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). They have different pathogenesis but similar presentation. Both carry a very poor five-year survival of 17% compared with more common cancers such as colorectal (60%), prostate (88%) and breast cancer (86%). The UK has the highest incidence of OAC in Europe in females and the second highest in males.

Oesophageal cancer is twice as common in men than

women with peak incidence at presentation in the 65-75 age group. Smoking is a major risk factor for oesophageal cancer and is linked to an estimated two-thirds of cases in the UK. Other risk factors include excess alcohol intake, chewing betel leaf, gastro-oesophageal reflux disease, obesity and Barrett's oesophagus.

Oesophageal cancer commonly presents with dysphagia

or odynophagia and can be associated with weight loss and vomiting. Referral for urgent endoscopy should always be considered in the presence of dysphagia regardless of previous history or medication. Dysphagia, weight loss and age are strong positive predictors of cancer. In a study on symptom referral for rapid access endoscopy, 92% of patients with malignancy had either dysphagia, weight loss or were over the age of 55 with other alarm symptoms. NICE recommends urgent referral (within 2 weeks) for direct access for upper GI endoscopy in patients with dysphagia and those aged 55 years or over with weight loss and any of the following: upper abdominal pain, reflux, or dyspepsia.

Once diagnosis has been confirmed, the staging process

enables patients and their doctors to choose appropriate treatments and avoid unnecessary surgery in those patients with advanced or incurable disease. Computed tomography of the neck, chest, abdomen and pelvis (whole body) is carried out initially to detect incurable disease. If the patient has no distant metastases or local invasion, a clinical assessment for curative treatment including surgery is carried out. Tumours that show local invasion or distant metastases are not amenable to curative treatment.

The majority of patients with oesophageal cancer have

incurable metastases at diagnosis. Palliative combination chemotherapy is an option in advanced oesophageal cancer. Dysphagia is the predominant symptom in patients with oesophageal cancer and self-expanding metal stents can be used to relieve dysphagia and aid nutrition. Nutritional assessment and review by a dietitian should be offered before, during and after radical treatment or palliative treatment.

Curative treatment

Advances in endoscopic imaging now result in detection of early, non-ulcerating carcinomas at screening and before dysphagia develops. In small nodular lesions < 2 cm, endoscopic mucosal resection (EMR) may be considered to stage and treat early cancers and differentiate between high grade dysplasia, T1a (tumour invades lamina propria or muscularis mucosae) and T1b (tumour invades submucosa) lesions.^{4,32} Endoscopic removal may be complete and considered curative in T1a given the low incidence of lymph node metastases in this group (< 5%), and avoids surgery. Although T1b OAC can be fully removed with EMR, patients should be offered radical resection if they are fit enough to have surgery due to the higher risk of lymph node metastases up to 20%.¹² Patients deemed medically fit with localised, non-metastatic OAC should be offered surgical resection. This is recommended with the addition of chemotherapy before or before and after surgery or chemoradiotherapy only before surgery.³

Curative chemoradiotherapy may be an option for localised OSCC especially if it is affecting the upper oesophagus. Although surgery appears to be a better option in comparison,³³ some studies have shown equivalent two-year survival to surgery in this group, therefore chemoradiotherapy remains a recommended first-line option for OSCC.^{18,34} The benefits, risks and treatment consequences of each option need to be fully discussed with the patient.

Oesophagectomy is highly invasive surgery and is performed by either an abdominal incision and trans-hiatal approach (to mobilise the stomach and a subsequent neck incision to pull up the stomach into the mediastinum and remove the oesophagus) or as a trans-thoracic Ivor-Lewis oesophago-gastrectomy which involves an abdominal incision and a left-sided thoracotomy. The two approaches have similar in hospital mortality and five-year survival rates.

Oesophagectomy is associated with significant morbidity and complications (33%),³⁵ in hospital mortality (1.9%) and 90-day mortality rate of (3.2%)³⁶ with reduction in long-term quality of life.³⁷ Surgery should be performed in centres with higher case volumes to achieve better results, and the outcomes of surgery are subject to significant national audit data.^{38,39}

Multiple meta-analyses have shown

the benefits of preoperative (neoadjuvant) chemotherapy or chemoradiotherapy in patients undergoing surgery.⁴ A large UK study found that two cycles of neoadjuvant chemotherapy improved survival over two years from 34 to 43% with no additional serious adverse events. This effect is notable especially for patients with T3 disease (tumour invades adventitia) or the presence of cancer in lymph nodes and is therefore used in most UK centres.⁴⁰⁻⁴²

Palliative treatment

The majority of patients presenting with oesophageal cancer have incurable metastases at diagnosis. A palliative treatment plan should be considered by the MDT, taking into account performance status and the views of the patient. Early direct involvement of the palliative care team, the cancer nurse specialists and dietitians is vital.

Palliative combination chemotherapy is an option in advanced oesophageal cancer. Studies have demonstrated a response to palliative chemotherapy in 37-48% of patients. Mean survival is 8-13 months with better outcomes in patients with OSCC.^{43,44} In patients with advanced OAC involving the upper stomach, endoscopic biopsies are assessed for HER-2 immunopositivity. The addition of trastuzumab can result in a significant improvement in response rate and median overall survival (13.8 vs 11.1 months) in those with HER-2 receptive tumours.^{45,46}

Self-expanding metal stents (SEMS) can be used to relieve dysphagia and aid nutrition. They can be placed endoscopically or radiologically bringing relief in a single procedure.¹⁸ When compared with other methods to help swallowing, such as endoscopy with argon photocoagulation debulking, SEMS have similar outcomes on quality of life, but debulking requires multiple procedures so is avoided in those patients with limited life expectancy.⁴⁷ Complications include stent migration, pain for up to 10 days, blockage and stent overgrowth by tumour requiring further stent or endoscopy in a third of cases.⁴⁸ External beam radiotherapy should be considered after SEMS insertion for long-term disease control.³

Support and follow-up

Nutritional assessment and review by a dietitian should be offered before, during and after radical or palliative treatment.³ Input from dietitians and cancer nurse specialists has been

shown to contribute to a faster recovery from treatment and improved quality of life.⁴⁹ Regular review of patients following therapy is essential to manage post-treatment side effects such as dysphagia and post-surgical diarrhoea and pain. Nutrition and psychological support should be included in these visits.⁴ Follow-up and radiological surveillance should not be offered solely for the detection of recurrence.³

The cancer nurse specialist acts as the patient's advocate and can ensure close liaison with primary and secondary care and help avoid readmission for relief of pain, nutrition and dysphagia.⁵⁰

CONCLUSION

Oesophageal cancer still has one of the lowest cancer survival outcomes in the UK and a low threshold for early endoscopy for dysphagic symptoms is recommended. Although cancer registries across Europe report gradual improvements in five-year survival rates, they are still generally poor and varied.

The observed trends reflect the variations in alcohol consumption, tobacco smoking and obesity across different countries.⁵¹ Preventative strategies including smoking cessation and weight reduction will improve rates of oesophageal cancer.

Advances in minimal access surgery and developments in endoscopy are encouraging.⁵²

Competing interests: None

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