

## Early diagnosis of oesophageal cancer improves outcomes

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Dr Andrew D Hopper  
MD FRCP  
Gastroenterology Consultant

Dr Jennifer A Campbell  
MRCP  
Clinical Fellow in Gastroenterology

Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK



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## AUTHORS

**Dr Andrew D Hopper**  
MD FRCP  
Gastroenterology  
Consultant

**Dr Jennifer A Campbell**  
MRCP  
Clinical Fellow in  
Gastroenterology

Department of  
Gastroenterology, Royal  
Hallamshire Hospital,  
Sheffield, UK

## FIGURE 1

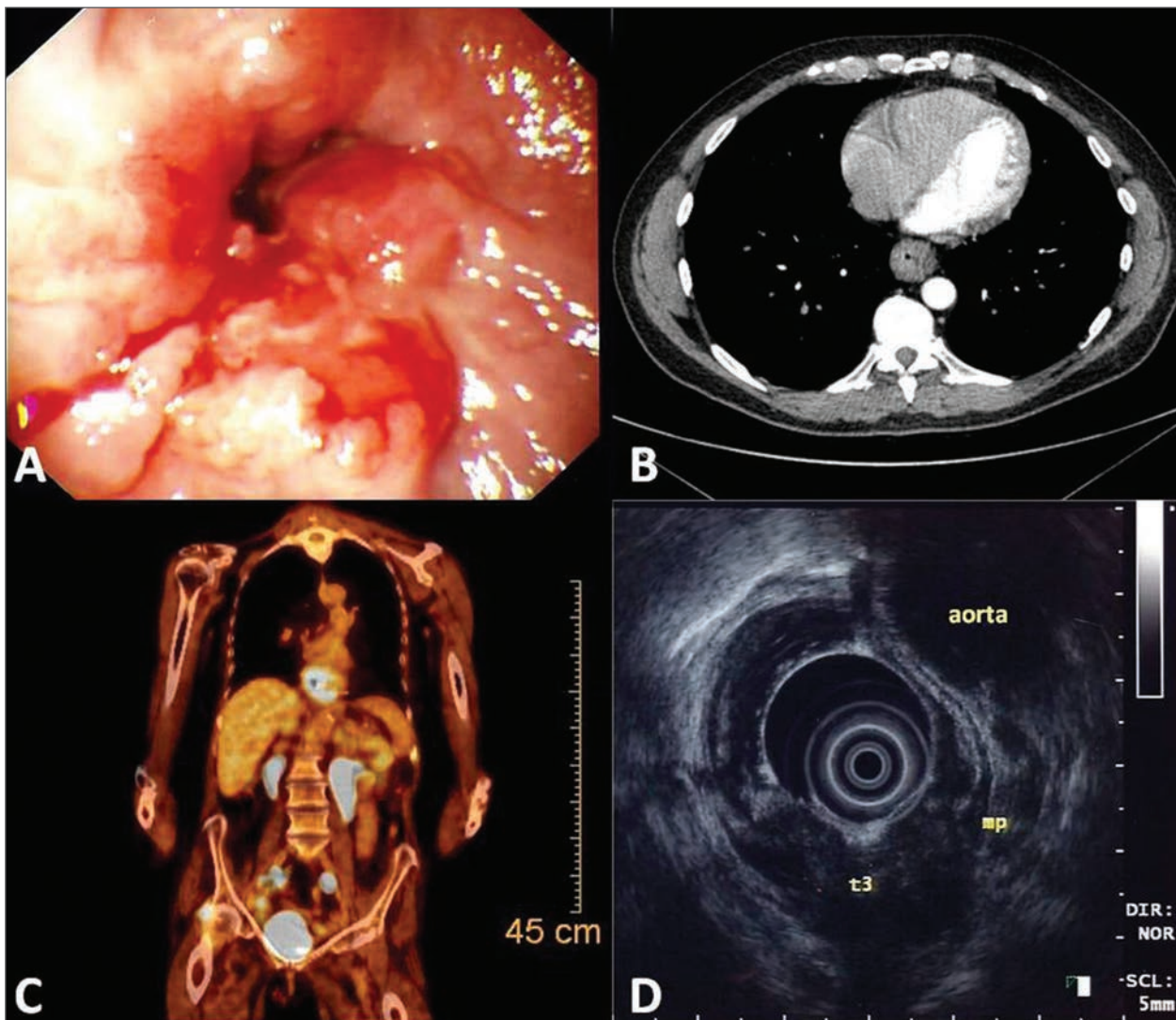
Oesophageal cancer staging:

**A** Advanced lower oesophageal adenocarcinoma diagnosed at endoscopy in a patient with dysphagia

**B** Subsequent CT showing thickened oesophageal tumour with no metastatic disease but close to the aorta

**C** PET CT imaging to identify metastatic disease showing hot tumour above the diaphragm

**D** Endoscopic ultrasound assessment showing T3 tumour breaching the muscularis propria (mp) but not invading the aorta



**What** are the risk factors for cancer of the oesophagus?

**Which** patients should be referred for endoscopy?

**What** are the management approaches?



**MORE THAN 7,000 CASES OF OESOPHAGEAL CANCER WERE DIAGNOSED IN 2013 MAKING IT THE TWELFTH**

most common cancer in the UK. However, its poor outcome makes it the sixth most common cause of cancer deaths.<sup>1</sup>

There are two main types, oesophageal squamous cell carcinoma (OSCC) and

oesophageal adenocarcinoma (OAC). Although their pathogenesis differs they present in the same manner. Both carry a very poor five-year survival of 16% when compared with more common cancers such as colorectal (59%), prostate (84%) and breast cancer (88%).<sup>2</sup> Worryingly, the UK has the highest incidence of OAC in Europe and has seen a 38% increase in cases in the

past three years.<sup>3,4</sup> OAC is now the more common form of oesophageal cancer seen in the UK, Australia and other Western developed countries. OSCC remains more common globally.

Like many cancers, improved survival requires early diagnosis. This review focuses on symptom recognition and risk factors to initiate early endoscopy referral and diagnosis that improves >>

the outcome of this potentially curable cancer. Current evidence regarding available and appropriate treatment options are then reviewed.

## ‘The UK has the highest incidence of oesophageal adenocarcinoma in Europe’

### RISK FACTORS

UK cancer registration statistics show a 2:1 male to female ratio for oesophageal cancer. Peak incidence at presentation is in the 65-75 age group, with 95% of cases presenting in those over the age of 50.<sup>3</sup> Smoking is a major risk factor for both types of oesophageal cancer and is linked to an estimated 66% of cases in the UK.<sup>3</sup> OSCC is linked to alcohol, smoking and chewing betel quid.<sup>4</sup> OAC is associated with the presence of GORD and its duration<sup>5</sup> and obesity (especially increased waist circumference).<sup>6</sup> Metaplastic change in the distal

oesophagus from recurrent acid reflux damage, known as Barrett’s oesophagus, is a precursor and risk factor for OAC. The risk of developing OAC with Barrett’s oesophagus is currently 0.1-0.33% per year.<sup>7,8</sup> Diagnosis of Barrett’s oesophagus generally triggers endoscopic surveillance to enable early diagnosis in the event of cancer developing which improves survival.<sup>9</sup> GORD has been discussed in a previous review article in this journal.<sup>10</sup>

### SUSPICIOUS SYMPTOMS

Oesophageal cancer commonly presents with dysphagia or odynophagia (pain with swallowing). This can be associated with weight loss and vomiting. Other important causes of dysphagia are listed in table 1, below, but referral for urgent endoscopy should still be considered in the presence of dysphagia regardless of previous history or medication. The significance of dysphagic symptoms was highlighted in a recent study based on symptom referral for rapid access endoscopy. Dysphagia, weight loss and age were strong positive predictors for

cancer. In this study, 92% of patients with malignancy had either dysphagia, weight loss or were over the age of 55 with other alarm symptoms (see table 2, opposite).<sup>11</sup> Although involuntary or unintentional weight loss has been defined as greater than 5% of body weight in over six months, in clinical practice objective markers are rarely available therefore any subjective history of weight loss in the absence of any known illness should be considered given its importance.<sup>12,13</sup>

## ‘Referral for urgent endoscopy for dysphagia should be considered regardless of previous history or medication’

Because of the elasticity of the oesophagus, advanced tumours can present without dysphagic symptoms. Anaemia (lesion bleeding), hoarse voice (early mediastinal invasion) or weight loss (metastatic spread) may manifest. At-risk or alarm symptoms for oesophago-gastric cancer have been identified in guidelines by NICE,<sup>14</sup> SIGN<sup>15</sup> and the British surgical and gastroenterological societies.<sup>16</sup>

## ‘Advanced tumours can present without dysphagic symptoms’

The NICE recommendations for endoscopy referral to assess for suspected oesophageal cancer in their recently updated guidelines are shown in table 2, opposite.

These guidelines differ slightly from other earlier guidelines regarding who to refer urgently or to consider for non urgent endoscopy. SIGN recommends early endoscopy for patients with dysphagia, recurrent vomiting, anorexia, weight loss or gastrointestinal (GI) blood loss regardless of age<sup>15</sup> and 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.<sup>16</sup>

**Table 1**

### Causes of dysphagia<sup>51</sup>

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

Given that the NICE guidance is the most up to date it should probably be used to guide the urgency of referral.

However, patients over 55 with dyspepsia should be fully reviewed to assess for the 'full' response to treatment. Given the current lack of other accurate diagnostic tests and the low complication rate of upper GI endoscopy non urgent referral for endoscopy is acceptable when any clinical suspicion is raised, persisting upper GI symptoms are unexplained or proton pump inhibitor (PPI) treatment is required long term (> six weeks).

## CONFIRMING DIAGNOSIS

### Endoscopy

Upper GI endoscopy with biopsy is the recommended investigation for patients with dysphagia to confirm oesophageal cancer. Lesional biopsy with histological interpretation is required to identify cancer subtype and exclude other causes such as severe gastro-oesophageal reflux and ulceration, see table 1, opposite.

Repeat gastroscopy should be performed if histology is benign and endoscopic appearances were suspicious of cancer. In cases of severe reflux, gastroscopy with biopsies is

repeated after six weeks of anti-acid treatment to ensure healing and exclude underlying cancer or Barrett's oesophagus. Despite improved advances in endoscopic imaging, failure to diagnose gastric cancer at initial endoscopy is consistently around 10%. Therefore patients with unexplained symptoms may require a second gastroscopy.<sup>17,18</sup> The principal factors associated with repeat gastroscopy include failing to suspect malignancy and misdiagnosing reflux oesophagitis or a peptic stricture at the first examination. Failure to take adequate biopsies can result in false-negative histology.

**Table 2**

### NICE recommendations for referral for direct access upper gastrointestinal endoscopy to assess for oesophageal cancer<sup>14</sup>

#### Offer urgent direct access upper GI endoscopy for:

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

#### Consider non-urgent upper GI endoscopy for:

- Haematemesis
- Aged 55 or over with:
  - Treatment-resistant dyspepsia\* or
  - Upper abdominal pain with low haemoglobin levels or
  - 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

\* Note BSG guidance suggests referral for urgent endoscopy in any patient > 55 with dyspepsia regardless of treatment response or presence of any other symptoms (see text)

**Table 3**

### Tumour, Nodal, Metastases classification of oesophageal cancer<sup>52</sup>

#### Primary tumour (T)

<b>T1a</b>	Tumour invades lamina propria or muscularis mucosae
<b>T1b</b>	Tumour invades submucosa
<b>T2</b>	Tumour invades muscularis propria
<b>T3</b>	Tumour invades adventitia
<b>T4a</b>	Tumour invades pleura, diaphragm or pericardium
<b>T4b</b>	Tumour invades aorta, spine or trachea

#### Regional lymph nodes (N)

<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in 1-2 regional lymph nodes
<b>N2</b>	Metastasis in 3-6 regional lymph nodes
<b>N3</b>	Metastasis in 7+ regional lymph nodes

#### Distant metastasis (M)

<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

## 'Endoscopy with biopsy is recommended for dysphagia to confirm oesophageal cancer'

Over the counter availability of ranitidine and PPI medication means that patients may well be taking an anti-acid medication at presentation. Initial gastroscopy should follow a break in PPI therapy, although there is no evidence to suggest the best timing, two weeks is usually suggested. PPIs may mask endoscopic findings and 'heal' malignant ulcers or alter their appearance. Barium studies can be performed if the patient is too unwell or keen to avoid gastroscopy.<sup>19</sup> Sensitivity of barium is reasonable for detecting malignancy but does not allow histological sampling to differentiate between malignant and benign ulceration and diagnosis can be delayed.

## CANCER STAGING

If a lesion suspicious of oesophageal cancer is seen at gastroscopy, the patient is warned and referral to a specialist upper GI surgery unit is made.

A thorough staging process is undertaken to allow patients to choose appropriate treatments and avoid patients with advanced or incurable disease undergoing unnecessary, significant surgery, see figure 1, p23. Oesophageal cancer staging employs the Tumour, Nodal, Metastases (TNM) classification system, see table 3, left.<sup>20</sup>

Computed tomography (CT) of the chest abdomen and pelvis is performed initially to detect incurable disease >>



**Table 4**

**Staging of oesophageal cancer using the Tumour, Nodal, Metastases classification and associated five-year survival despite treatment (slightly simplified to account for both types)<sup>52</sup>**

Stage	Five-year survival		Tumour (T) Nodal (N) Metastases (M) stages
	OAC	OSCC	
IA	78%	70%	T1, NO, MO (well differentiated)
IB	64%	61%	T1, NO, MO (poorly differentiated)
IIA	50%	53%	T2, NO, MO
IIB	40%	41%	T3, NO, MO; T2, N1, MO; T1, N1, MO
IIIA	25%	25%	T4a, NO, MO; T3, N1, MO; T1 or 2, N2, MO
IIIB	18%	18%	T3, N2, MO
IIIC	15%	15%	T4a, N1, 2 or 3, MO; T4b, Any N, MO
IV	< 4%	<4%	Any T, Any N, M1

and would usually be requested at the time of a suspicious endoscopy. It has a high (90%) sensitivity for detecting distant metastases > 1 cm and significant local invasion into adjacent mediastinal organs (85-100%).<sup>21-23</sup>

If distant metastases and local invasion are absent, a clinical assessment is required to discuss findings and assess suitability for curative treatment including surgery. Given the potential significant surgery, detailed below, and the likely age at presentation, a formal objective cardio-respiratory assessment is often required including exercise tolerance<sup>24</sup> or complex cardiopulmonary exercise testing.<sup>2</sup>

Patients choosing curative treatment undergo complete TMN staging, see table 3, p25. Endoscopic ultrasound (EUS) provides accurate assessment of the tumour size and local lymph node stage. This is important as tumours with early T stage (1-2) do not benefit from neoadjuvant chemotherapy before curative resection (see treatment section below).<sup>26</sup>

Positron emission tomography (PET) using F-18 fluorodeoxyglucose is also performed to detect distant lymph node or metastatic disease. Around 5% of patients with oesophageal cancer who are initially thought operable are precluded from oesophagectomy after CT and EUS staging.<sup>27</sup>

Staging laparoscopy is indicated where the tumour involves the lower oesophagus and upper stomach and CT shows potentially operable disease. Laparoscopy can detect peritoneal and metastatic disease under 5 mm in

diameter, and enables peritoneal cytology and biopsies to be obtained from suspicious lesions. Staging laparoscopy changes treatment decisions for invasive surgery in up to 28% of patients with gastric cancer after CT.<sup>28</sup> As with all cancers the stage of a cancer is closely related to prognosis emphasising the need to diagnose oesophageal cancer at an early stage, see table 4, above.<sup>29</sup>

The staging process highlights the complex pathway and investigations required before reaching a decision regarding suitability for curative surgery and treatment. If needless significant abdominal and thoracic surgery is performed in patients with advanced disease the recovery from surgery is likely to have a huge impact on the patient's quality of life for their remaining life expectancy. Throughout the staging process it is imperative that patients are supported by cancer nurse specialists.

**MANAGEMENT**

Management options are discussed at a specialist upper GI multidisciplinary team (MDT) meeting involving experienced surgeons, radiologists, pathologists, oncologists and cancer nurse specialists. Investigation results are considered alongside the patient's fitness for surgery and/or chemotherapy and the final decision made together with the patient after the clinician has explained the recommended treatment options.

Tumours that show local invasion (T4) or distant metastases (M1) are not amenable to curative treatment.

**Curative treatment**

Patients deemed medically fit with non-metastatic or locally invasive tumours should be offered surgical resection to cure early cancers (Stage I-IIA) and chemotherapy (neoadjuvant) followed by surgical resection for higher stage tumours (Stage IIB+) as it improves long-term survival.<sup>16</sup>

An oesophagectomy is performed by either an abdominal incision and transhiatal 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 transthoracic Ivor-Lewis Oesophago-gastrectomy which involves an abdominal incision and a left-sided thoracotomy.

Both methods have been found to have similar hospital mortality and five-year survival rates. This highly invasive surgery is associated with significant morbidity and complications (30%), hospital mortality (2.9%)<sup>30</sup> and reduction in long-term quality of life<sup>31</sup> therefore results of surgery are subject to national audit<sup>30</sup> and performed in centres with higher case volumes to achieve better results.<sup>32</sup>

**'Most patients with oesophageal cancer have incurable metastases at diagnosis'**

Multiple meta-analyses have shown the benefits of preoperative (neoadjuvant) chemotherapy or radiotherapy in patients undergoing surgery. Two cycles of neoadjuvant chemotherapy have been shown to improve survival over two years from 34 to 43% without additional serious adverse events in a large UK Medical Research Council study. This effect is notable especially for patients with T3 disease or the presence of lymph nodes and is therefore used in most UK centres.<sup>33-35</sup>

Given its response to radiotherapy, definitive (curative) chemoradiotherapy can be an option for localised OSCC (i.e. all areas within a radiation field) especially if it is affecting the upper oesophagus. Although surgery seems to be a better option in comparison,<sup>36</sup> some studies have shown equivalent two-year survival to surgery in this group, therefore chemoradiotherapy remains a recommended first-line option for OSCC.<sup>37,16</sup>

# key points

SELECTED BY

Dr Phillip Bland

GP, Dalton-in-Furness

**There are two main types of oesophageal cancer,** oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). Although their pathogenesis differs they present in the same manner. Both carry a very poor five-year survival of 16%. In the UK there is a 2:1 male to female ratio for oesophageal cancer. Peak incidence at presentation is in the 65-75 age group, with 95% of cases presenting in those over 50. Smoking is a major risk factor for both types of oesophageal cancer and is linked to an estimated 66% of cases in the UK. OSCC is linked to alcohol, smoking and chewing betel quid. OAC is associated with the presence of GORD and its duration and obesity (especially increased waist circumference).

**Oesophageal cancer commonly presents with dysphagia** or odynophagia (pain with swallowing). This can be associated with weight loss and vomiting. All patients with recent onset dysphagia should be referred for rapid access endoscopy. Referral for urgent endoscopy should still be considered in the presence of dysphagia regardless of previous history or medication. Dysphagia is not always present therefore all patients with alarm symptoms should be considered for endoscopy.

**NICE recommends referral for urgent direct access upper** GI endoscopy to assess for oesophageal cancer for: *Dysphagia* **or** *Aged 55 and over* with weight loss and any of the following: upper abdominal pain; reflux; dyspepsia. Non urgent direct access upper GI endoscopy should be considered for: *Haematemesis*; **or** *Aged 55 or over* with: treatment-resistant dyspepsia **or** upper abdominal pain with low haemoglobin levels **or** 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.

**Patients over 55 with dyspepsia should be fully** reviewed to assess for the 'full' response to treatment. Non urgent referral for endoscopy is acceptable when any clinical suspicion is raised, persisting upper GI symptoms are unexplained or proton pump inhibitor treatment is required long term (> 6 weeks).

**Patients deemed medically fit with non-metastatic or** locally invasive tumours should be offered surgical resection to cure early cancers (Stage I-IIA) and chemotherapy (neoadjuvant) followed by surgical resection for higher stage tumours (Stage IIB+) as it improves long-term survival.

**Most patients presenting with oesophageal cancer** have incurable metastases at diagnosis. A palliative treatment plan should be considered. Palliative combination chemotherapy can be offered in advanced oesophageal cancer. Self-expanding metal stents can be used to aid dysphagia and nutrition.

Advances in endoscopic imaging now result in detection of early, non-ulcerating carcinomas at screening before dysphagia develops. In small nodular lesions < 2 cm, endoscopic mucosal resection may be considered to stage and treat early cancers and differentiates between high-grade dysplasia, T1a and T1b lesions. 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.

## Palliative treatment

Most 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 patient preference. Early direct involvement of the palliative care team, the cancer nurse specialists and dieticians (all core members of the MDT) is essential.

Palliative combination chemotherapy can be offered in advanced oesophageal cancer. Trials have shown response to palliative chemotherapy in 37-48% of patients. Mean survival ranges from 8 to 13 months with better outcomes in OSCC groups.<sup>38,39</sup> 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 statistically significant improvement in response rate and median overall survival (13.8 versus 11.1 months) in patients with HER-2 receptive tumours.<sup>40,41</sup>

Dysphagia is the predominant symptom in patients with oesophageal cancer. Self-expanding metal stents (SEMS) can be used to aid dysphagia and nutrition. They can be placed endoscopically or radiologically in a single procedure.<sup>16</sup> When SEMS are compared with other methods to help swallowing, such as endoscopy with argon photocoagulation debulking, they have similar outcomes on quality of life, but debulking requires multiple procedures so is avoided in those patients with limited life expectancy.<sup>42</sup> Complications of SEMS are stent migration, pain for up to ten days, blockage and stent overgrowth by tumour requiring further stents or endoscopy in one third of cases.<sup>43</sup> Dilatation is rarely used because of the high risk of perforation and early recurrence and percutaneous endoscopic gastrostomy placement is only rarely used.

## SUPPORT AND FOLLOW-UP

Dietician review and cancer nurse specialist input has been demonstrated to contribute to improved quality of life.<sup>44</sup> The cancer nurse specialist is central to patient care, consulting with multiple specialties including primary care to provide a co-ordinated approach and act as the patient's advocate.<sup>45</sup> Regular review of patients following therapy is required to manage post-treatment side effects such as dysphagia and post-surgical diarrhoea and pain.

Regular access to cancer nurse specialists has been shown to be cost effective in supporting follow-up.<sup>46</sup>

In the palliative setting these nurses can ensure close liaison with primary and secondary care and help avoid readmission for relief of pain, nutrition and dysphagia.<sup>47</sup>

## FUTURE DIRECTIONS

The assessment and evaluation of outcomes is fundamental in the management of oesophageal cancer. The National Oesophago-Gastric Cancer Audit has set high standards.<sup>30</sup> With drivers like this it is encouraging to see cancer registries across Europe reporting gradual improvements in five-year survival rates, however, they are still generally poor and varied.

The observed trends reflect the variations in alcohol consumption, smoking and obesity across European countries.<sup>48</sup> With the incidence remaining high we need to develop effective treatments with limited morbidity that minimise significant effects on quality of life and health service resources. Minimal access surgery and developments in endoscopy are encouraging.<sup>49</sup>

Preventative strategies to improve rates of oesophageal cancer including smoking cessation and weight reduction are required in the UK. Increasing expertise and evidence for treating early lesions in Barrett's oesophagus mean less invasive endoscopic techniques can be used to prevent cancer development.<sup>50</sup>

Given the advanced stage of oesophageal cancer at presentation, waiting for patients to develop alarm symptoms before referring them for endoscopy would seem not to improve our five-year survival rates. There are currently very limited non-invasive biomarkers to detect or screen for early oesophageal cancer. Research to develop a novel approach to early diagnosis of Barrett's oesophagus and dysplasia using a swallowed cell collection device (Cytosponge), coupled with molecular assays is in



development and may hold a possible option for future screening.<sup>53</sup>

In the meantime 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.

**Further reading**

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**Useful information**

**Cancer Research UK**  
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[www.macmillan.org.uk](http://www.macmillan.org.uk)

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[editor@thepractitioner.co.uk](mailto:editor@thepractitioner.co.uk)