

Oesophageal cancer

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The incidence of oesophageal cancer is increasing. While the incidence of squamous cell carcinoma of the oesophagus has recently been stable or declined in Western societies, the incidence of oesophageal adenocarcinoma has risen more rapidly than that of any other cancer in many countries since the 1970s, particularly among white men.¹ The UK has the highest reported incidence worldwide, for reasons yet unknown.² Overall, the prognosis for patients diagnosed with oesophageal cancer is poor, but those whose tumours are detected at an early stage have a good chance of survival. We outline strategies for prevention and describe presenting features of oesophageal cancer to assist generalists in diagnosing and referring patients early. Treatment is often highly invasive and alters patients' quality of life. We review the evidence from large randomised clinical trials, meta-analyses, and large cohort and case-control studies (preferably those of population based design, since they carry a lower risk of selection bias).

Who gets oesophageal cancer?

The two main histological types of oesophageal cancer, adenocarcinoma and squamous cell carcinoma (fig 1), have different causes and patterns of incidence.¹ Although the incidence of adenocarcinoma has surpassed that of squamous cell carcinoma in many Western countries, squamous cell carcinoma still represents 90% of all oesophageal cancer cases in most Eastern countries. Register based cohort studies have found that the incidence of oesophageal cancer increases with age and the average age of onset is about 65 to 70 years. Generally, men are more affected than women: the striking 7:1 male predominance of oesophageal adenocarcinoma remains unexplained.¹

The origins of oesophageal cancer are multifactorial, including interactions among environmental risk expo-

SOURCES AND SELECTION CRITERIA

We searched PubMed to identify peer reviewed original articles, meta-analyses, and reviews. Search terms were oesophageal cancer, cancer of the oesophagus, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, neoplasm and oesophagus, and oesophageal neoplasm. Only papers written in English were considered. We mainly included studies published during the recent few years where we deemed the scientific validity to be adequate.

sures and nucleotide polymorphisms of inflammatory and tumour growth promoting pathways. The two main risk factors for oesophageal adenocarcinoma are gastro-oesophageal reflux and obesity.³ Some gene-environment interaction patterns differ between patients with and without reflux.⁴ Polymorphisms of genes coding for the obesity linked insulin-like growth factor may also be markers of risk.⁵

The two main risk factors for squamous cell carcinoma of the oesophagus are tobacco smoking and high alcohol consumption, particularly in combination. The 3:1 male predominance is explained by differences in such exposures between the sexes. Infection with the bacterium *Helicobacter pylori*, which commonly occurs in the gastric mucosa, seems to reduce the risk of oesophageal adenocarcinoma by about half.⁶ A possible mechanism is that the gastric atrophy that might follow such infection reduces the acidity and volume of the gastric juice, thereby lowering the risk of gastro-oesophageal reflux.⁷

Use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) might decrease the risk of oesophageal cancer. A recent meta-analysis, mainly including case-control studies, showed a 35% decrease in the risk of oesophageal cancer among users of NSAIDs compared with non-users.⁸ Factors affecting the choice of using NSAIDs, however, constitute a threat to the validity of observational studies, as highlighted in some investigations.^{8,9}

How does a patient with oesophageal cancer present?

The cardinal symptoms of oesophageal cancer are progressive dysphagia and weight loss. The dysphagia is typically linked with vomiting of undigested food. Earlier symptoms may include discomfort or occasionally pain when swallowing. If such symptoms persist they should prompt an upper endoscopy. However, elasticity of the oesophagus means that onset of symptoms may not occur

SUMMARY POINTS

The incidence of oesophageal adenocarcinoma has increased during the past few decades, particularly among white men in the UK

Oesophageal adenocarcinoma is associated with gastro-oesophageal reflux and obesity, whereas squamous cell carcinoma is associated with use of tobacco and alcohol

Diagnosis is confirmed by endoscopy with biopsies, precise tumour stage is defined by more sophisticated radiological examinations

A multidisciplinary approach is recommended in decision making and treatment

Curatively intended treatment usually includes chemotherapy or radiochemotherapy followed by extensive surgery

The overall prognosis for oesophageal cancer patients remains poor and several palliative options are available where cure is not possible

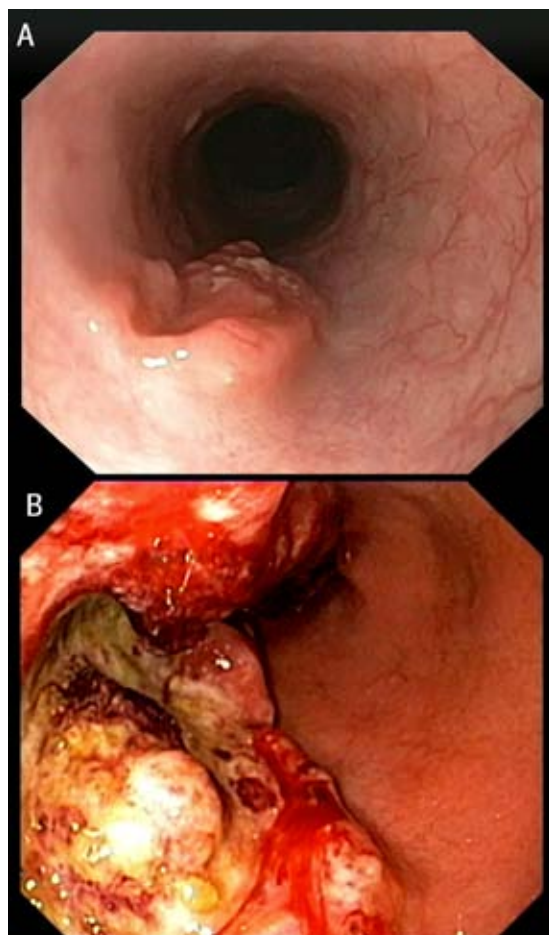


Fig 1 | (A) Small oesophageal squamous cell carcinoma seen on endoscopy. (B) Large necrotic and bleeding oesophageal adenocarcinoma seen on endoscopy. Used with permission from Dr Edgar Jaramillo

until the tumour is at an advanced stage. Late symptoms include hoarseness, caused by tumour overgrowth of the left laryngeal nerve, severe cough linked with tumour fistula between the oesophagus and the respiratory tract, and signs of metastatic disease—for example, ascites or palpable lymph node metastases.

How is the diagnosis made?

Figure 2 shows a flowchart for diagnosis.

Referral

Patients presenting with symptoms indicative of oesophageal cancer should undergo urgent endoscopy, preferably within one week. Patients with typical symptoms together with macroscopic signs of tumour on endoscopy require immediate referral (without need for histological confirmation) to a unit with relevant experience, usually an upper gastrointestinal surgery unit.

Primary tumour

The diagnosis is made by visualising a mass on endoscopy and by histological confirmation using biopsy samples collected from the mass and adjacent tissue. Figure 1 shows typical oesophageal cancer lesions as seen on endoscopy.

The importance of staging

Accurate staging allows for individually tailored treatment and the tumour needs to be staged before a treatment decision can be made. Recent advances in imaging techniques have contributed to more accurate staging. Cohort studies have shown that fluorodeoxyglucose combined positron emission tomography combined with computed tomography can be used to visualise early distant spread of tumours.¹⁰ This tool has also shown promising results in the evaluation of the effects of preoperative oncological treatment.¹¹ Endoscopic ultrasonography can accurately measure the extent of local and regional tumour growth, which helps with staging.¹² More recently, endoscopic mucosal resection has become a useful staging technique for early intramucosal tumours. These tools have led to improved staging and less referral of patients with advanced or incurable disease for aggressive treatment.

Can oesophageal cancer be prevented?

Primary prevention

Avoidance of obesity, tobacco smoking, and alcohol intake decrease the risk of oesophageal cancer. Gastro-oesophageal reflux could also be reduced by controlling obesity and tobacco smoking, which are the two main established risk factors for reflux.

Secondary prevention

The hypothesis that antireflux medication and antireflux surgery reduce the incidence of oesophageal adenocarcinoma in people with reflux has been addressed mainly

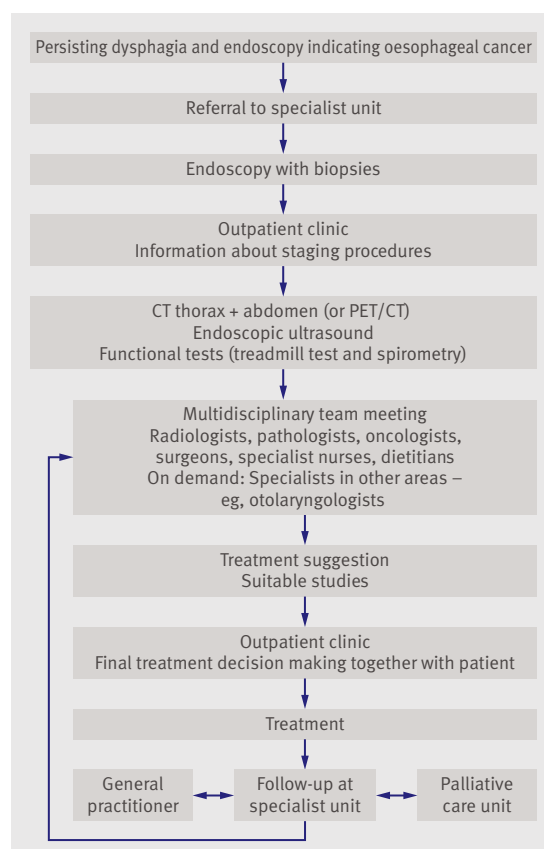


Fig 2 | Diagnosis with multidisciplinary team for cancer of the oesophagus suitable for curatively intended surgery

TIPS FOR NON-SPECIALISTS

- The cardinal symptoms of oesophageal cancer are progressive dysphagia and weight loss
- Any persisting dysphagia in adults should prompt an urgent endoscopy
- Typical symptoms in combination with an endoscopy indicating oesophageal cancer should be followed by referral to a unit with experience in the treatment of this tumour
- A majority of patients with oesophageal cancer need initial palliative therapy, usually provided at the referral hospital, and thereafter general palliative care

in uncontrolled studies. Robust data (from randomised trials, for example) supporting a preventive effect of antireflux medication against cancer are limited.^{13 14} A large population based cohort study found no reduction in the risk of oesophageal adenocarcinoma with time after antireflux surgery.¹⁵ The potential preventive effect of NSAIDs needs to be evaluated in randomised trials.

Is there a role for endoscopic screening?

Endoscopic screening for early oesophageal cancer requires selection of an easily identifiable high risk group. One such group might be white men with severe reflux and obesity. However, the feasibility of screening has to be based on the individual's absolute risk, which takes the incidence of the cancer into account. The high prevalence of reflux and the low incidence of oesophageal adenocarcinoma make endoscopic screening programmes of people with reflux symptoms, with or without known risk factors, unfeasible.³ Moreover, there are no data showing a reduction in deaths from oesophageal adenocarcinoma resulting from endoscopic screening.¹⁶ A better defined and much smaller, truly high risk group needs to be identified before any endoscopic screening can be considered. Measures other than endoscopy could be used for such screening in the future—for example, ingestible oesophageal sampling devices such as the Cytosponge.¹⁷ The role of endoscopic surveillance of Barrett's oesophagus, a metaplasia associated with oesophageal adenocarcinoma, has been addressed in a recent review.¹⁸

What is the approach to making a decision about treatment?

Patients with invasive oesophageal cancer need to be thoroughly evaluated regarding fitness and tumour stage. Tumours with local overgrowth into adjacent tissues or organs (T4) or with distant metastases (M1) are usually not eligible for curatively intended treatment. Physical activity, biological age, and comorbidities are considered when patient fitness is evaluated, and treadmill tests and spirometry are used whenever needed to objectively assess fitness. The final treatment recommendation should be based on a multidisciplinary meeting, as shown in figure 2, in which experienced doctors representing surgery, oncology, radiology, and pathology should participate. A multidisciplinary review of the radiology examinations, pathology reports, and the objective and subjective fitness of the patient could improve the accuracy of the treatment decisions and facilitate inclusion into clinical trials.^{19 20} The final decision must thereafter be taken together with the patient. The doctor responsible for the patient must thoroughly explain the reasons for the recommendation of the meeting. If there are doubts about this recommen-

dation, a second opinion from a multidisciplinary team in another hospital is valuable.

What is the best approach to organisation of care?

The optimal treatment of patients with oesophageal cancer requires the resources and skills of a well coordinated multidisciplinary team (fig 2). Increased centralisation of treatment for patients with cancer of the oesophagus puts additional strain on resources at large centres, and these patients have high needs for supportive care.²¹ Such circumstances emphasise the need for good coordination and continuity of the complex care pathway. A randomised clinical trial has emphasised the important role of specialised contact nurses in maintaining and coordinating the care pathway.²² These nurses ideally keep in close contact with each patient and take part in all appointments with them.

Treatment with intent to cure—what are the options?

Treatment with a curative intent is undertaken only in patients who are considered fit enough to undergo extensive surgery and who have a tumour without any signs of overgrowth or distant metastases. The most common tumour stages among resected oesophageal cancer patients are advanced primary cancer without invasion into surrounding tissue or organs (T2-T3) with local or regional lymph node metastases (N1).²³

Surgical resection remains the main option for curative treatment. Whether to offer chemotherapy or chemoradiotherapy before surgery is controversial because underpowered trials have produced contradictory results. Although the majority of individual studies do not show any benefit from such a strategy, data from more recent and larger randomised clinical trials indicate that preoperative chemotherapy or chemoradiotherapy improve survival compared with surgery alone.^{24 25} Moreover, data from case series indicate a curative potential for chemoradiotherapy alone without surgery, particularly in older non-surgical candidate patients, but randomised trials are needed to support a nonsurgical strategy.²⁶ Nevertheless, chemoradiotherapy alone is used in many patients who are not fit enough for surgery or in those who choose not to undergo surgery. Currently, a typical treatment strategy in fit patients with the most commonly occurring tumour stages (II-III) is chemotherapy followed by surgery.²⁵

Surgical resection*Which is the preferred surgical approach?*

Oesophageal cancer surgery is an extensive procedure with substantial risk of postoperative complications and long term morbidity.²⁷ A recent review concluded that fit patients are possibly best treated by a transthoracic oesophagectomy with removal of local and regional lymph nodes and vessels along with the oesophageal specimen (extended en bloc, two field lymphadenectomy). However, for patients who are less fit or those with junctional tumours or tumours of the gastric cardia, a transhiatal approach with a partly blunt dissection in the chest (through an abdominal and neck incision, without opening the thoracic wall) with a neck anastomosis may be a better option.²⁸

Where to have surgery?

Since the in-hospital mortality after oesophagectomy is lower when centres and surgeons are experienced in this procedure, centralisation to high volume units has taken place in recent years.²¹ Much of the lower risk of mortality at centres dealing with high volumes of such cases seems to be explained by better handling of complications.²⁹ The risk of complications seems, however, to be more related to the skills of the individual surgeon than to volume alone.³⁰

How to improve quality of life outcomes?

Large, population based cohort studies have shown that patients who undergo surgical resection of an oesophageal tumour have poor health related quality of life in the short and long term.²⁷ These findings highlight a need to improve the procedure—for example, by better tailoring of surgery, and through the development of less invasive techniques such as minimally invasive, robotic, and vagal nerve preserving oesophagectomy.^{31–33} Such developments must, however, be based on results from large multicentre randomised clinical trials that are well designed rather than on case series. Generally, patients undergoing surgical resection should be enrolled in a randomised trial when possible.

Endoscopic treatments

Various endoscopic approaches are emerging as potential alternatives to surgical treatment in the highly selected group of patients with high grade dysplastic mucosa and early intramucosal oesophageal cancer.^{34–35} Such local procedures might be justified in view of the low likelihood of lymph node metastases in early tumours, but more research is needed before general clinical recommendations can be given. Endoscopic mucosal resection, photodynamic therapy, argon plasma coagulation, and radiofrequency ablation can all induce regression of dysplasia.¹⁴ A large randomised trial found that radiofrequency ablation resulted in eradication rates of 94% in patients with dysplasia, compared with a sham treatment,³⁵ and it might become the endoscopic treatment of choice, combined with endoscopic mucosal resection for visible, focal lesions. Until longer term trials become available, however, radiofrequency ablation should only be used in expert centres with careful follow-up.¹⁴ For the vast majority of patients with an invasive tumour, endoscopic therapy is, at least currently, not a treatment option.

Who will get palliative care and what will it involve?

Large population based cohort studies estimate that up to 75% of patients with oesophageal cancer are never treated with a curative intent, mainly because of

PALLIATIVE THERAPY

May include all or any of the following:

- Endoscopic stenting
- Brachytherapy
- Chemotherapy
- External radiotherapy
- Feeding through gastrostomy, jejunostomy, or intravenously
- Pain relief
- Best palliative supportive care

QUESTIONS FOR FUTURE RESEARCH

- Interaction between risk exposures and genetic factors might improve knowledge of the causes of oesophageal cancer
- Identification of preventive measures might decrease the incidence of oesophageal cancer
- Identification of true high risk groups for oesophageal cancer might provide possibilities for feasible future surveillance strategies
- Curative and palliative treatment of oesophageal cancer needs to be improved, and is best achieved through large randomised clinical trials

advanced tumour stage or poor physical condition.²³ For incurable disease, patients need the support of expert palliative care professionals who are familiar with the pros and cons of the available palliative treatments. Several approaches can improve health related quality of life in patients who are ineligible for surgery (box), and the best approach involves treatment that is tailored to offer the best possible outcome for the patient. Patients with advanced oesophageal cancer have a short median survival and thus are no longer offered surgical resection for palliation only. A major challenge is to relieve dysphagia as effectively as possible. A recent Cochrane systematic review of interventions aimed at relieving dysphagia concluded that self expanding metallic stents and intraluminal brachytherapy (local radiotherapy) seem to offer the best palliation.³⁶ Chemotherapy and external beam radiotherapy can also palliate dysphagia. We stress that a well functioning care pathway is just as important for patients in whom the aim of therapy is palliation, as it is for those where curatively intended treatment is possible. Support from a palliative care team, including, for example, pain therapy, feeding, or general support, is valuable for these patients.

Is the prognosis for patients with oesophageal cancer improving?

Population based cohort studies have shown that the overall prognosis for patients with cancer of the oesophagus has improved slightly during the past 20 years.³⁷ However, despite efforts to improve surveillance, diagnostic procedures, and treatment, the overall five year survival in oesophageal adenocarcinoma remains lower than 15%.³⁷ Population based studies from Europe have shown the five year survival after curatively intended surgery for oesophageal adenocarcinoma to be 30–35%, a figure that has improved substantially during the past few years, whereas the population based five year survival for stage specific tumours has been reported to be 67%, 33%, and 8% in stages 0–I, II, and III, respectively.²³ Unfortunately, patients with tumour recurrence after surgery cannot usually be cured because of the lack of effective second line treatment.

Which might be the future directions?

Primary prevention by avoidance of preventable risk exposures might help to reduce the incidence of oesophageal cancer in the future. It should also be possible to identify true high risk patients for oesophageal cancer who might benefit from tailored surveillance strategies, possibly by

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- Extracorporeal life support (*BMJ* 2010;341:c5317)
- Managing diabetic retinopathy (*BMJ* 2010;341:c5400)

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Cancer Research UK (www.cancerresearchuk.org)—UK's leading cancer charity's website, containing information about the charity and about cancer

For patients

Oesophageal Patients Association (www.opa.org.uk)—A large support group for patients with oesophageal cancer

Patient UK (www.patient.co.uk)—Comprehensive source of health and disease information for patients

Cancer Research UK (www.cancerresearchuk.org)

British Society of Gastroenterology (www.bsg.org.uk/patients/patients/general/oesophageal-cancer.html)—Patient information from a large gastroenterology organisation

combining risk factor information with future genetic markers that might predict a risk of progression.

Improvements in the treatment of oesophageal cancer, in regard to survival and to health related quality of life, are best achieved through large randomised clinical trials to investigate new chemotherapeutic agents and new, less invasive, surgical approaches.

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COMMENTARY

Managing oesophageal cancer in a resource poor setting—a Malawian example

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The incidence of cancer of the oesophagus is increasing worldwide.¹ Countries with adequate resources now have a range of diagnostic and treatment options for patients with this disease; unfortunately the situation in resource poor settings is hugely different.

Oesophageal cancer is the sixth most common cancer in Malawi² with almost equal proportions in men and women. By contrast with western Europe, adenocarcinoma is rare; more than 90% of patients present with squamous cell carcinoma. Accepted risk factors such as smoking and alcohol (especially home brewed spirit) play a part in the pathogenesis of this condition in Africa, as elsewhere, but other factors need to be considered—human papillomavirus infection, nitrosamines from open fire cooking, and aflatoxins from stored maize.³

The clinical scenario is discouraging; patients present late with long standing, progressive dysphagia, many of them unable even to swallow their own saliva. Diagnostic facilities are limited. At a district level a simple barium swallow may be possible, but endoscopy is available only in the central hospitals. Patients need to be referred for this investigation, often to a distant centre where endoscopy lists are overcrowded and pathology services limited. As a result months are lost between the first symptoms and the final diagnosis. For disease staging only chest radiographs and abdominal ultrasounds are readily available and computed tomography scan is rarely an option.

The weight loss attendant on the late presentation and the combination of common co-morbidities (HIV/AIDS, tuberculosis, malnutrition, cardiac and renal diseases) conspire against any attempt at curative resection. The Queen Elizabeth Central Hospital is the biggest government referral hospital in Malawi and in our series of

around 250 patients newly diagnosed with oesophageal cancer annually at endoscopy on average not more than 10 were considered suitable for major surgery. Even when surgery is possible, other constraining factors exist; lack of intensive care beds, shortage of blood, and oversubscribed operating lists. Radiotherapy and chemotherapy are not available, and palliative care unsurprisingly has a major role.

We have adopted self expanding metal stents as the only available management option. Over the last year, in a charity funded trial, we were able to purchase and insert 220 stents in three of the central hospitals in Malawi. The outcome is still being assessed but so far palliative treatment has been quite successful with a median survival rate of more than seven months and improvement in quality of life. After stent insertion patients are encouraged to make regular visits to our palliative care clinic for further support.

We need to address the long treatment delays suffered by patients with a clinically apparent diagnosis. Awareness campaigns for early detection and improved facilities for surgery are essential if the suffering of our patients is to be reduced.

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