BMJ Best Practice

Oesophageal cancer

Straight to the point of care

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Summary

Oesophageal cancer incidence is increasing across the developed world. Men are considerably more likely than women to develop the disease.

The two main histological types are squamous cell carcinoma and adenocarcinoma. In the developed world, adenocarcinomas predominate.

Low socioeconomic status, smoking, excessive alcohol use, GORD, Barrett's oesophagus, and obesity are some of the main risk factors.

Tumours are often locally advanced at the time of diagnosis. Accurate staging is important for prognosis and treatment planning.

Superficial intramucosal well-differentiated oesophageal cancer can be managed with an oesophagus-sparing approach utilising endoscopic resection and surveillance. Localised tumours that are not amenable to endoscopic resection, those with poor differentiation, lymphovascular invasion, or deeper submucosal invasion are often best treated by oesophagectomy.

For locally advanced disease, combined modality therapy is considered the current standard. This involves chemotherapy or chemoradiotherapy followed by surgery.

Patients without a complete pathological response following resection may benefit from adjuvant immunotherapy.

Targeted therapies can be used in patients with metastatic oesophageal and oesophageal junction cancer.

Treatment decisions for patients with recurrent or refractory disease are informed by prior treatment history and multidisciplinary tumour board discussions.

Definition

Most oesophageal cancers are neoplastic mucosal lesions that originate in the epithelial cells lining the oesophagus.

Oesophageal cancers are usually squamous cell carcinomas or adenocarcinomas.

Rarely, other cancers, such as melanoma, sarcoma, small cell carcinoma, or lymphoma, can occur in the oesophagus.

THEORY

Epidemiology

Oesophageal cancer is the eleventh most common type of cancer worldwide and constitutes the seventh leading cause of cancer deaths.[6] Cancers of the oesophagus account for over 440,000 cancer deaths annually, which represents 4.6% of all global cancer deaths.[6]

In the US in 2024, there will have been an estimated 22,370 new cases of oesophageal cancer (median age at diagnosis 68 years) and an estimated 16,130 people will have died of this disease.[7][8] [9] Between 2016 and 2020, there were 4.2 new cases of oesophageal cancer per 100,000 men and women per year in the US. The age-adjusted rate of new cases of oesophageal cancer during this timeframe was 7.1 per 100,000 in men, and 1.7 per 100,000 in women.[7]

Age-standardised incidence of oesophageal cancer is higher across Eastern Asia and Eastern Africa, with the highest incidence seen in Malawi.[6] It is the leading cause of cancer death among men and women in Bangladesh and among men in Malawi and Botswana.[6] Hypotheses to explain geographical variation include genetic predisposition and disparity in the prevalence of dietary and environmental risk factors across regions.[10] [11]

Oesophageal adenocarcinoma (OAC)

Rapidly becoming the most prevalent type in developed countries.[10] In the US, approximately 70% of cases are adenocarcinomas.[2] The vast majority of the increase in incidence of adenocarcinoma of the oesophagus is attributed to the rise of Barrett's oesophagus in young, otherwise healthy men - particularly in white people in the US and Western Europe.[12] [13] Rising rates of obesity have been identified as a likely causal factor for this increase; obesity contributes to the development of gastro-oesophageal reflux disease, a major underlying cause of Barrett's oesophagus.[14] [15] Cancer registries indicate that the Netherlands, United Kingdom, and Ireland have the highest age-standardised incidence of OAC.[11]

Oesophageal squamous cell carcinoma (OSCC)

OSCC continues to be the most prevalent type worldwide; incidence of OSCC has been reported to be higher in non-white people.[16] [17] In the US, squamous cell carcinoma is more common than adenocarcinoma within the black population, with the incidence rate in black men being 4.5 times higher than that of white men.[10] [18] It is commonly associated with alcohol and tobacco consumption.[6] OSCC has become less common in the West in recent decades due to reduced alcohol and tobacco use; it now accounts for less than 30% of all oesophageal cancers in the US and Western Europe.[14]

Malawi, Mongolia, and Kenya have the highest age-standardised incidence of OSCC.[11]

Aetiology

The risk of oesophageal cancer increases with age.[19]

Male sex is a risk factor for both oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC).[20] [21] Approximately 70% of cases occur in men.[6][7] The difference cannot be accounted for by other risk factors (e.g., gastro-oesophageal reflux disease [GORD], obesity), as these are equally divided between the sexes.[22]

Achalasia is associated with an increased risk for OAC and OSCC.[23] [24]

Tobacco smoking strongly increases the risk of OSCC and moderately increases the risk of OAC.[25] Current smokers have a ninefold increased risk of OSCC compared with non-smokers.[26] Smoking increases the risk of OAC and oesophago-gastric junction adenocarcinoma approximately two- to threefold.[26] [27]

Lower socioeconomic status is associated with a two- to fourfold increase in risk of oesophageal cancer.[25]

Factors implicated in the development of OAC

Barrett's oesophagus

- Metaplasia of the mucosal lining of the distal oesophagus caused by long-standing gastro-oesophageal reflux. Barrett's oesophagus is a pre-malignant condition for the development of OAC.[28] People with Barrett's oesophagus have a 30 to 60 times greater risk of developing OAC compared with the general population.[29]
- Risk of progression from Barrett's oesophagus to OAC is correlated with the degree of dysplasia present. The annual progression rate of low-grade dysplasia to high-grade dysplasia or OAC is 4%; the annual risk of progression from high-grade dysplasia to OAC is 25%.[30]
- A familial form of Barrett's oesophagus has been described, with multiple reports of familial clustering of patients with the condition. In a database analysis of patients diagnosed with Barrett's oesophagus or OAC in the Netherlands, 7% of cases were familial. These cases have a younger average age of onset of reflux symptoms and diagnosis of OAC than non-familial cases, suggesting a possible inherited predisposition to Barrett's oesophagus and/or OAC in some people.[31]

GORD

- One population-based case-control study found that people with GORD had a sevenfold increased risk of developing OAC, compared with people without GORD.[32] More frequent, more severe, and longer-lasting symptoms were associated with a higher risk of cancer.[32]
- Use of theophyllines or anticholinergic medications to relax the lower oesophageal sphincter has been associated with a modestly increased risk of OAC, although the association may be confounded by the presence of concomitant asthma or chronic obstructive lung disease.[33]

Hiatus hernia

- The presence of a hiatus hernia increases risk of OAC twofold to sixfold, most probably by increasing gastro-oesophageal acid reflux.[25]

Body mass index (BMI)

- Elevated BMI is a risk factor for OAC, irrespective of the presence of GORD.[34] [35] [36] [37]
- Case-control studies demonstrate a dose-dependent relationship between increasing BMI and risk of OAC.[37] [38]
- An inverse association between BMI and risk for OSCC has been reported.[34] [36] [39] [40]

Dietary factors

- Diets high in total fat, saturated fat, and cholesterol appear to be associated with an increased risk of OAC.[41] [42]

Factors implicated in the development of OSCC

Alcohol consumption

- Relative risk (RR) for OSCC is increased for heavy drinkers compared with non-drinkers and occasional drinkers (RR 4.95, 95% CI 3.86 to 6.34).[43]

- There appears to be a synergistic effect in the presence of tobacco smoke.[44] [45]

Human papillomavirus (HPV)

- Meta-analyses report an association between HPV infection (serotypes 16 and 18) and incidence of OSCC.[46] [47] [48] [49]
- An aetiological association between HPV infection and oesophageal cancer has not been demonstrated.[50] [51]

Vitamin and mineral deficiencies

- Vitamin and mineral deficiencies may contribute to increased risk for oesophageal cancer in some regions.[52] [53]

Race

- Incidence of OSCC has been reported to be higher in non-white people.[16] [17]
- In the US, squamous cell carcinoma is more common than adenocarcinoma within the black population, with the incidence rate in black men being 4.5 times higher than that of white men.[10] [18]

Family history of oesophageal or other cancer

- In one population-based cohort-control study, cumulative risk of oesophageal cancer to age 75 was 12.2% among first-degree relatives of OSCC cases and 7.0% in those of controls (hazard ratio [HR] 1.91, 95% CI 1.54 to 2.37).[54]
- Increased risk for OSCC has been associated with a family history of any cancer.[55]

Maté consumption

- Drinking maté, a herbal infusion, is associated with an increased risk for OSCC.[56] [57] Polycyclic aromatic hydrocarbons and thermal injury have been implicated.[25]

Hot beverages

- Habitual consumption of very hot drinks (as occurs in some cultures in Iran, China, Kenya, and elsewhere) has been associated with increased risk for OSCC, by repeated thermal injury.[58] [59] [60] [61]

Poor oral hygiene

- Case-control studies have demonstrated an association between OSCC and poor oral hygiene, irrespective of alcohol and tobacco use.[62] [63] [64]

Hereditary cancer syndromes

- Tylosis (also known as focal non-epidermolytic palmoplantar keratoderma [PPK] or Howel-Evans syndrome) is a rare autosomal dominant syndrome caused by germline mutations in the RHBDF2 gene. It is associated with an increased lifetime risk of developing OSCC, with an average age of diagnosis of 45 years. Routine screening by upper gastrointestinal endoscopy is recommended for patients and their family members starting from 20 years of age.[15]
- Bloom syndrome is a rare autosomal recessive disorder caused by a mutation in the BLM gene, which codes for the DNA repair enzyme RecQL3 helicase.[65] It is associated with an increased risk of developing multiple cancers, especially lymphoma and acute myeloid leukaemia, lower and upper gastrointestinal tract neoplasias (including OSCC), skin cancers, and cancers of the genitalia and urinary tract.[65] Screening for GORD (with or without endoscopy to detect early oesophageal cancer) may be considered.[15]
- Fanconi anaemia (FA) is an autosomal recessive condition caused by germline mutations in any one of at least 21 genes associated with the FA pathway, which has a role in DNA repair. It presents

with congenital abnormalities, progressive pancytopenia, and a predisposition to cancer (both haematological malignancies and solid organ tumours, particularly squamous cell carcinomas, including OSCC).[66] Upper gastrointestinal endoscopy may be considered as a screening strategy.[15]

Pathophysiology

Oesophageal cancer arises in the mucosa of the oesophagus. It then progresses locally to invade the submucosa and the muscular layer. Metastasis typically occurs to the peri-oesophageal lymph nodes, liver, and lungs.

Squamous cell carcinoma primarily affects the upper and middle oesophagus. Cancers of the lower oesophagus and oesophago-gastric junction are typically adenocarcinomas.[3]

The pathophysiological mechanisms of many causes are not yet fully elucidated and are the subject of active research. However, mechanisms have been proposed for some of these aetiological factors.

Alcohol

- The exact mechanism by which alcohol causes oesophageal cancer is not yet known. Alcohol itself does not bind DNA, is not mutagenic, and does not cause cancer in animals. However, it may act through its conversion to acetaldehyde (a known carcinogen), acting as a solvent for other carcinogens, and causing nutritional deficiencies.
- After ingestion, ethanol is converted to acetaldehyde by alcohol dehydrogenase (ADH) enzymes, and is then detoxified to acetate by acetaldehyde dehydrogenase (ALDH).
- In addition to systemic absorption and metabolism, in heavy drinkers (>40 g/day), alcohol in the saliva is also oxidised to acetaldehyde by the many microbes in the mouth, and by the salivary glands and mucous membranes. This process is intensified in those with poor oral hygiene and high bacterial load. Detoxification in the mouth is limited, however, and the result is strikingly high local concentrations of carcinogenic acetaldehyde. Saliva is then swallowed, exposing the oesophageal mucosa.[45]
- In vitro, acetaldehyde causes point mutations in human lymphocytes, sister chromatid exchanges, and cellular proliferation, and inhibits DNA repair.

Tobacco

- Smoking exposes the body to a large number of carcinogens, such as polycyclic aromatic hydrocarbons, nitrosamines, and acetaldehyde, which are present in tobacco smoke.

Gastro-oesophageal reflux disease (GORD) and Barrett's oesophagus

- Chronic GORD causes metaplasia (Barrett's oesophagus) in which the stratified squamous epithelium that normally lines the distal oesophagus is replaced by abnormal columnar epithelium. Although this might seem a favourable adaptation to chronic reflux (because columnar epithelium appears more resistant to reflux-induced injury), these metaplastic cells may become dysplastic, and ultimately malignant, through genetic alterations that activate proto-oncogenes and/or disable tumour suppressor genes.
- Factors that increase gastro-oesophageal reflux damage, such as hiatus hernia, achalasia, obesity, or medications that lower the lower oesophageal sphincter tone, may further increase the risk of oesophageal carcinoma.[33] [67] [68] However, studies fail to consistently demonstrate increased risk associated with specific medications.[33]

THEORY

Classification

Histological classification

Diagnosis should be based on endoscopic biopsies with the histological tumour type classified according to the World Health Organization (WHO) criteria.[1] The two main histological types are oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), which together account for >95% of cases. In the US, approximately 70% of cases are adenocarcinomas (typically arising in Barrett's oesophagus).[2] OAC occurs mainly in the distal oesophagus and oesophago-gastric junction, while OSCC tends to affect the upper and middle oesophagus.[3] Rarely, other histological types, such as melanoma, sarcoma, small cell carcinoma, or lymphoma, can occur in the oesophagus.

Siewert classification

Siewert tumour type should be assessed in all patients with OAC involving the oesophago-gastric junction.[4] [5] The classification can be performed based on careful endoscopy with appropriate description of tumour length in relation to anatomical landmarks. Siewert classification allows comparison of data between various centres and facilitates the choice of surgical therapy. Tumours are classified into three types:

- Siewert Type 1: tumour of the lower oesophagus with the epicentre located within 1-5 cm above the anatomical oesophago-gastric junction
- Siewert Type 2: true carcinoma of the cardia with the tumour epicentre within 1 cm above and 2 cm below the oesophago-gastric junction
- Siewert Type 3: subcardial carcinoma with the tumour epicentre between 2 cm and 5 cm below the oesophago-gastric junction, which infiltrates the oesophago-gastric junction and lower oesophagus from below.

Siewert Type 1 and 2 tumours are treated as oesophageal cancer whereas Siewert Type 3 tumours are treated according to gastric cancer guidelines.

Case history

Case history #1

A 55-year-old man presents with severe dysphagia to solids and worsening dysphagia to liquids. His social history is significant for 40 pack-year cigarette smoking and a 6-pack of beer per day. He has lost over 10% of his body weight and currently is nourished only by milkshake supplements. He complains of some mild odynophagia and is constantly coughing up mucus secretions.

Case history #2

An otherwise healthy 45-year-old male executive complains of heartburn. He has tried over-the-counter medications with no relief. He took a course of proton pump inhibitors for 6 weeks, but still has heartburn. He has no weight loss or dysphagia.

Other presentations

Oesophageal cancer often presents in an insidious and non-specific manner, with indigestion, retrosternal discomfort, and dysphagia being the leading complaints. Often patients present late because they have compensated for dysphagia by eating softer foods or chewing their food more thoroughly. Patients may develop respiratory sequelae, primarily from aspiration but also from other causes, such as direct invasion of tumour into the tracheobronchial tree (usually involving the left main stem bronchus). Symptoms may include cough, dyspnoea, or pleuritic pain. Hoarseness can result from direct involvement of the recurrent laryngeal nerve.

Approach

Oesophageal cancer typically presents late, which in part contributes to the generally poor prognosis. Clinicians need to remain vigilant and investigate patients thoroughly in order to make the diagnosis at the earliest possible opportunity.

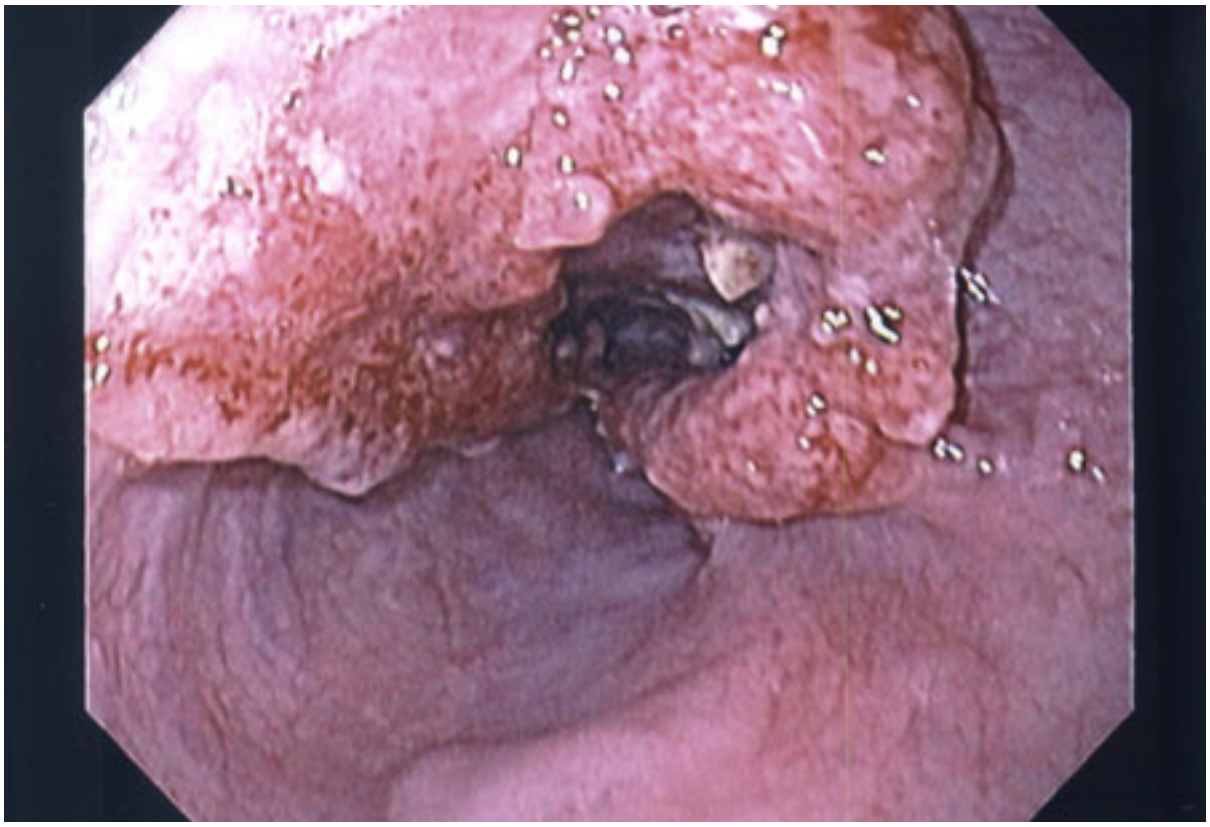
Clinical features

The most common presenting signs of oesophageal cancer are dysphagia and odynophagia. For patients with Barrett's oesophagus and early-stage adenocarcinoma of the oesophagus and oesophago-gastric junction, reflux is the most common presenting sign. Severe weight loss usually occurs after swallowing difficulties begin.[87]

Phrenic nerve involvement can trigger hiccups. A postprandial or paroxysmal cough may indicate the presence of an oesophago-tracheal or oesophago-bronchial fistula resulting from local invasion by a tumour.

Initial investigations

While a patient noting dysphagia is often evaluated first by videoesophagram, if oesophageal cancer is suspected an upper gastrointestinal endoscopy is warranted.[88]



Endoscopic view of oesophageal cancer

Personal collection of Mark J. Krasna

This allows assessment of any obstruction, and biopsy to confirm the histology of mucosal lesions. The minimal recommended number of biopsies is not defined, but accepted convention is to obtain ≥6 representative biopsies of the lesion.[88] The histological tumour type should be reported according to

the World Health Organization (WHO) criteria.[1] The differentiation between oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC) is of clinical and prognostic relevance. Immunohistochemical (IHC) staining is recommended in poorly differentiated and undifferentiated cancers when differentiation between OSCC and OAC using morphological features is not possible.[88] Less common tumour types, such as neuroendocrine tumours, lymphomas, mesenchymal tumours, melanomas, and secondary tumours must be identified separately from OSCC and OAC.[88]

Endoscopy can identify benign causes of obstructive symptoms as well as allow an opportunity for dilation and immediate relief of symptoms.

Laboratory investigations

Serum electrolytes and renal function testing should be performed in advanced cases with near or complete oesophageal obstruction. These patients may become severely volume-depleted and hypokalaemic because of their inability to swallow fluids and their own potassium-rich saliva.

Staging and prognostication

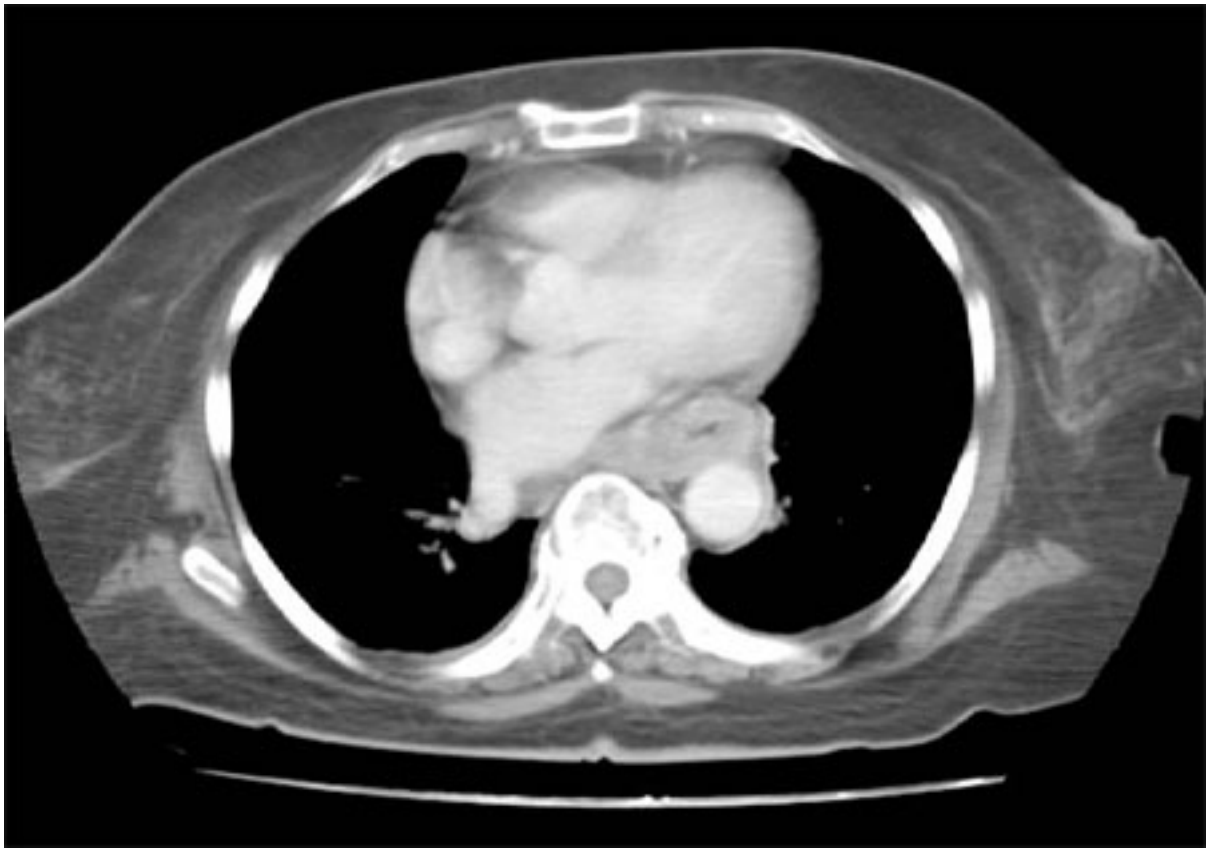
Computed tomography (CT) scan of the chest and abdomen is often performed if the suspicion of oesophageal cancer is high or biopsy confirms the diagnosis.[89] Obtaining a (18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan, and endoscopic ultrasound (EUS) forms the basis of accurate clinical staging.

EUS allows assessment of the depth of tumour infiltration into or through the oesophageal wall (T stage) and evaluates any concerning locoregional nodal disease. Metastatic disease, when present, is often in the lungs, liver, peritoneum, and/or bones and is best visualised on PET/CT. Lymph node spread is typically to the regional mediastinal lymph nodes, coeliac lymph nodes, para-aortic nodes, and cervical chain. In some countries, abdominal ultrasound is used instead of CT to diagnose metastasis to the liver or coeliac lymph glands.

T1 and T2 lesions generally show an oesophageal mass thickness between 5 mm and 15 mm, and T3 lesions show a thickness >15 mm. T4 lesions show invasion of contiguous structures on CT or EUS. This is occasionally suspected by the presence of 'contact' between the oesophagus and surrounding structures, such as the airway or the great vessels. In general, contact with the aorta of more than 90 degrees circumference is considered suspicious for T4 disease and invasion.[90]

Computed tomography (CT)

The CT scan plays a key role in assessing tumour bulk and in monitoring tumour response to therapy. CT can define whether the tumour has spread from the oesophagus to regional lymph nodes and/or contiguous structures, and indicate the presence of distant metastases.



CT scan showing T3 tumour at level of inferior pulmonary vein

Personal collection of Mark J. Krasna

Oral and intravenous contrast should be used to ensure optimal opacification of the lumen and visualisation of the heart, mediastinal vessels, and liver.[89] An oesophageal wall thickness >5 mm is abnormal, regardless of the degree of distension.

CT scans cannot accurately differentiate T1a (no submucosa involvement) disease and T1b (submucosa involvement) disease.[91]

Magnetic resonance imaging (MRI)

MRI is an alternative to CT for the staging of oesophageal cancer, particularly in detecting metastatic disease to visceral organs. It is highly accurate when assessing the liver or adrenals and for determining advanced local spread (T4). However, it is less reliable in defining early infiltration (T1 to T3).

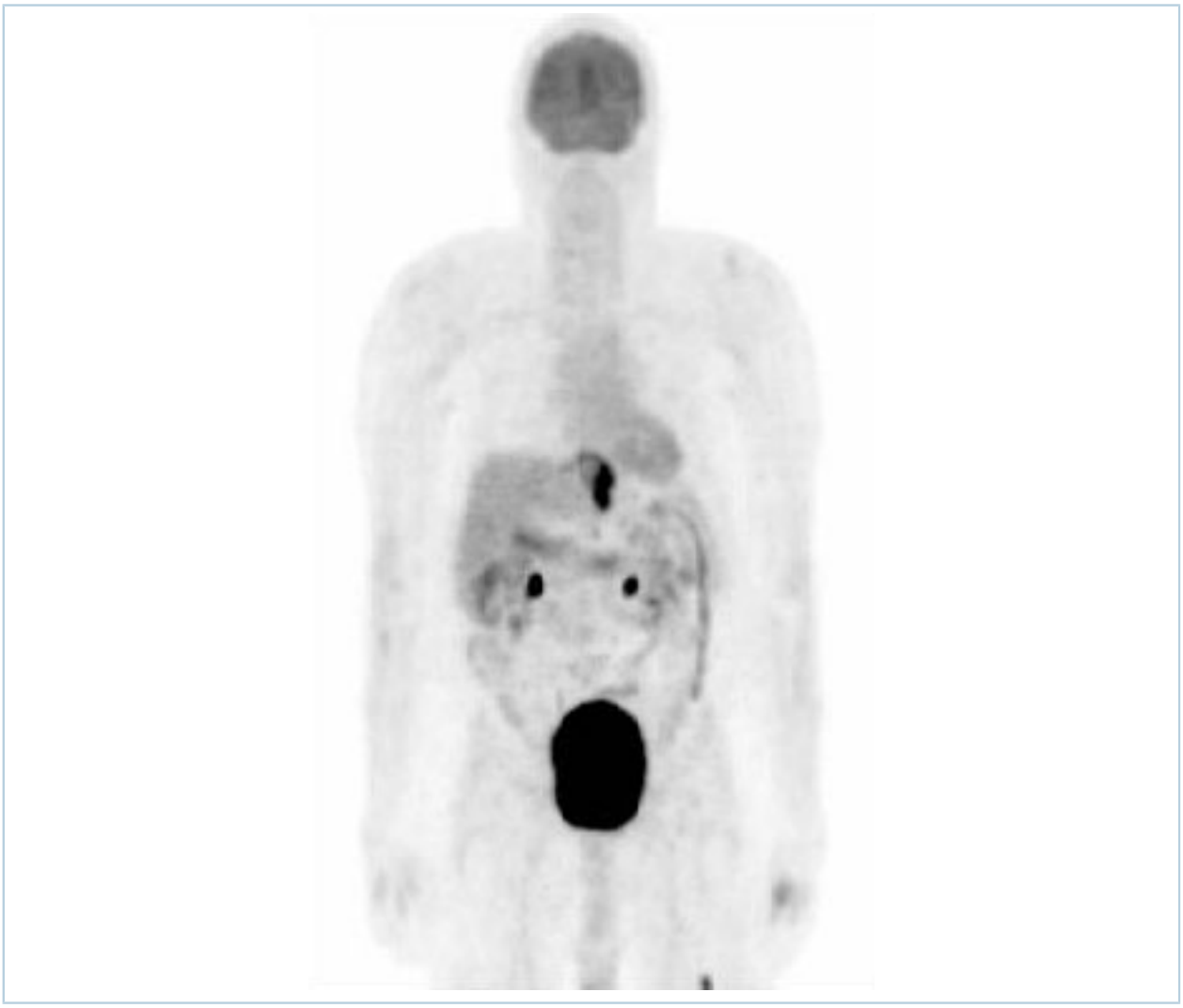
MRI appears to be sensitive in predicting mediastinal invasion; the loss of signal in the vessels and the air-filled trachea and bronchi may provide a clear delineation between the tumour and the aorta and the tracheobronchial tree. Like CT scans, MRI scans are poor at detecting tumours restricted to mucosa or submucosa, and also tend to under-stage the regional lymph nodes.[92]

(18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)

Use of FDG-PET improves the accuracy of staging and facilitates selection of patients for surgery, by detecting distant metastatic disease not identified by CT alone.[89] Positron emission tomography (PET) has a higher sensitivity than CT for detecting nodal and distant metastases, and a higher accuracy for determining resectability than CT. However, there is a high rate of false-positive FDG-PET findings, and

small locoregional nodal metastases (<8 mm) cannot be identified reliably by current PET technology.[15] [93]

PET can be used to detect responses to chemotherapy and radiotherapy.[94] [95] [96] In patients with oesophageal cancer, relative changes in FDG uptake can predict response to neoadjuvant therapy.[97] [98]



PET scan showing oesophageal cancer at the gastro-oesophageal junction. Note metastatic deposit in left femur

Personal collection of Mark J. Krasna

An FDG-PET scan is generally done before EUS to avoid unnecessary testing in patients with metastatic disease.[99]

Endoscopic ultrasound (EUS) ± fine needle aspiration (FNA)

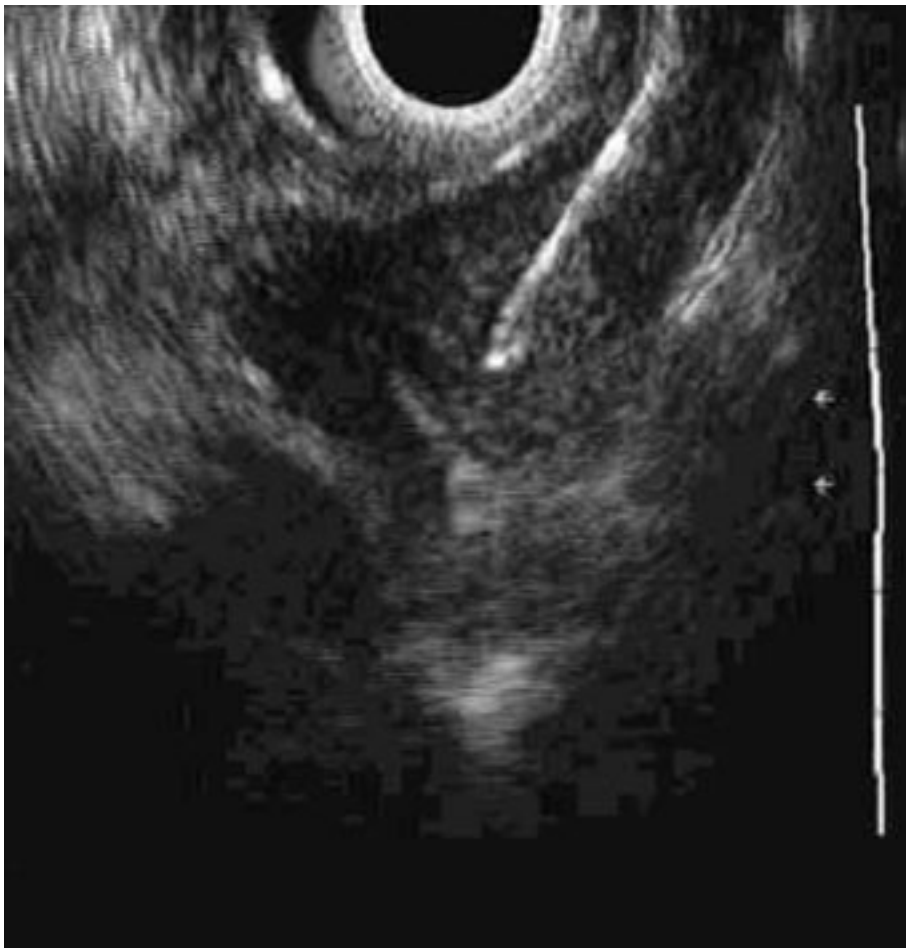
EUS combined with FNA (EUS/FNA) is the most accurate imaging modality for locoregional staging of oesophageal cancer prior to therapy. The overall accuracy of EUS/FNA in this setting is 87%; the comparable figure for EUS alone is 74%.[100] [101]

The accuracy of EUS in staging advanced oesophageal cancer appears to be greater compared with early cancer (sensitivity and specificity of EUS for staging oesophageal cancer: 81.6% and 99.4% in T1 tumours; 81.4% and 96.3% in T2 tumours; 91.4% and 94.4% in T3 tumours; and 92.4% and 97.4% in T4

tumours, respectively).[102] Evidence of lymph node involvement that is proven pathologically by EUS/FNA is considered definitive, and the patient can be referred for the appropriate stage-specific therapy.

EUS re-staging subsequent to neoadjuvant therapy lacks accuracy.[103] [104] This is believed to be a function of distortion of the architecture of the oesophageal wall arising from treatment-induced fibrosis and ulceration.

Residual nodal disease following neoadjuvant therapy is an ominous finding. EUS/FNA may have a role, but this may necessitate sampling all visible nodes regardless of criteria for suspiciousness.[105]



Endoscopic ultrasound-guided fine needle aspiration of lymph node

Personal collection of Mark J. Krasna

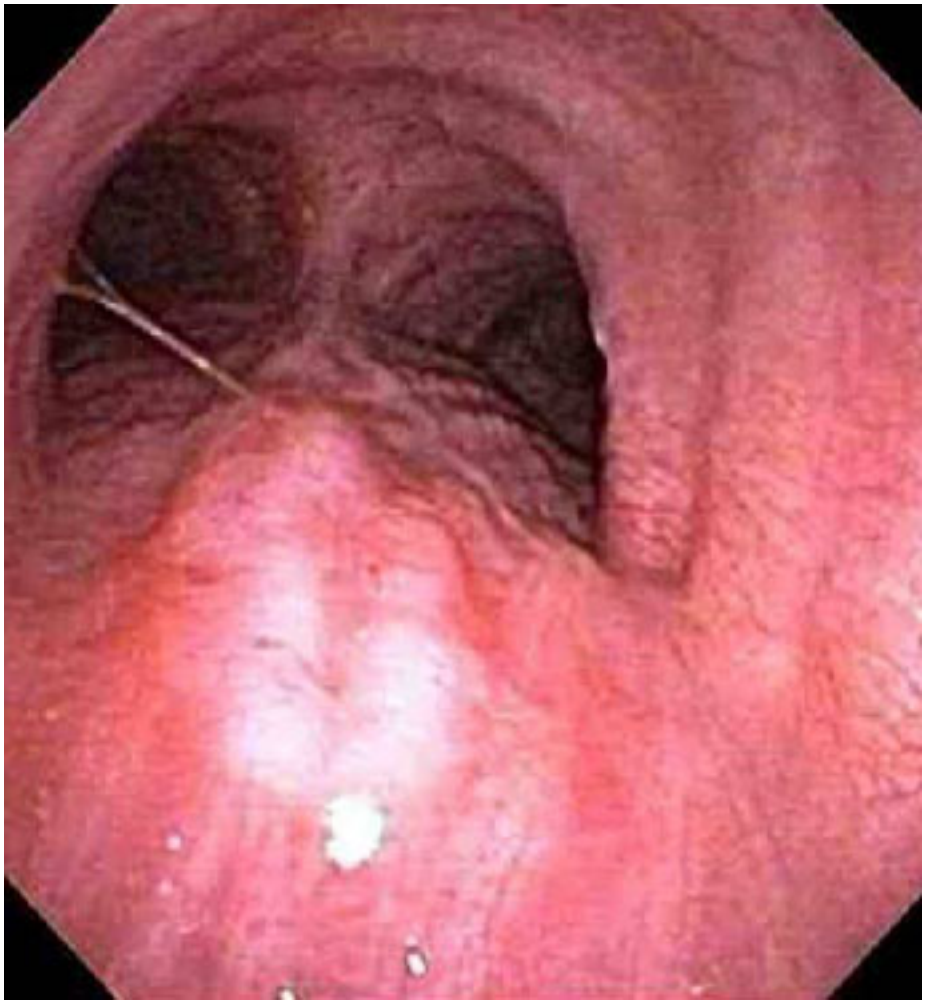
EUS findings that indicate a tumour that cannot be resected include invasion into the left atrium, wall of the descending aorta, spinal body, pulmonary vein or artery, or tracheobronchial system. The latter should be confirmed by bronchoscopy with transbronchial FNA. Stenosis can limit the clinical utility of EUS.[106]

Complications of EUS (with or without FNA) include perforation (0.02% to 0.08%), haemorrhage (0.13% to 0.69%), and infection (0.4% to 1.7%).[107]

Bronchoscopy

In patients with disease of the middle and upper thirds of the oesophagus, bronchoscopy with biopsy, FNA, or brushings can be helpful in determining involvement of the tracheobronchial tree. Bronchoscopy should be performed prior to considering surgery on tumours at these locations.

FNA can be performed into mucosal lesions within the lumen, or transbronchially into lesions adjacent to the airway.



Tracheal invasion (T4) confirmed by bronchoscopy

Personal collection of Mark J. Krasna

Thoracoscopy/laparoscopy

Thoracoscopic or laparoscopic staging is rarely needed but may be appropriate in selected patients; for example, those with adenocarcinoma of the oesophagus or oesophagogastric junction with significant extension into the cardia.[108] European Society for Medical Oncology (ESMO) guidelines recommend laparoscopy in patients with locally advanced (T3/4) adenocarcinomas of the oesophago-gastric junction to rule out peritoneal metastases (which are found in approximately 15% of patients). Tumours extending more than 4 cm beyond the gastro-oesophageal junction are at particular risk for peritoneal disease. The finding of otherwise unknown metastases may spare patients from undergoing futile surgery.[88] Studies indicate that thoracoscopy and laparoscopy may improve accuracy compared with non-invasive testing in these situations.[109] [110]

Clinical examination of the head and neck region

A qualified clinical examination of the head and neck region is recommended in patients with OSCC to exclude concurrent head and neck second primary tumours (HNSPTs). The pooled prevalence of HNSPTs in patients with OSCC is 6.7%, and prognosis of patients with an additional HNSPT is worse

than for patients with only OSCC. Early detection of HNSPTs may improve the outcome for patients with OSCC.[88]

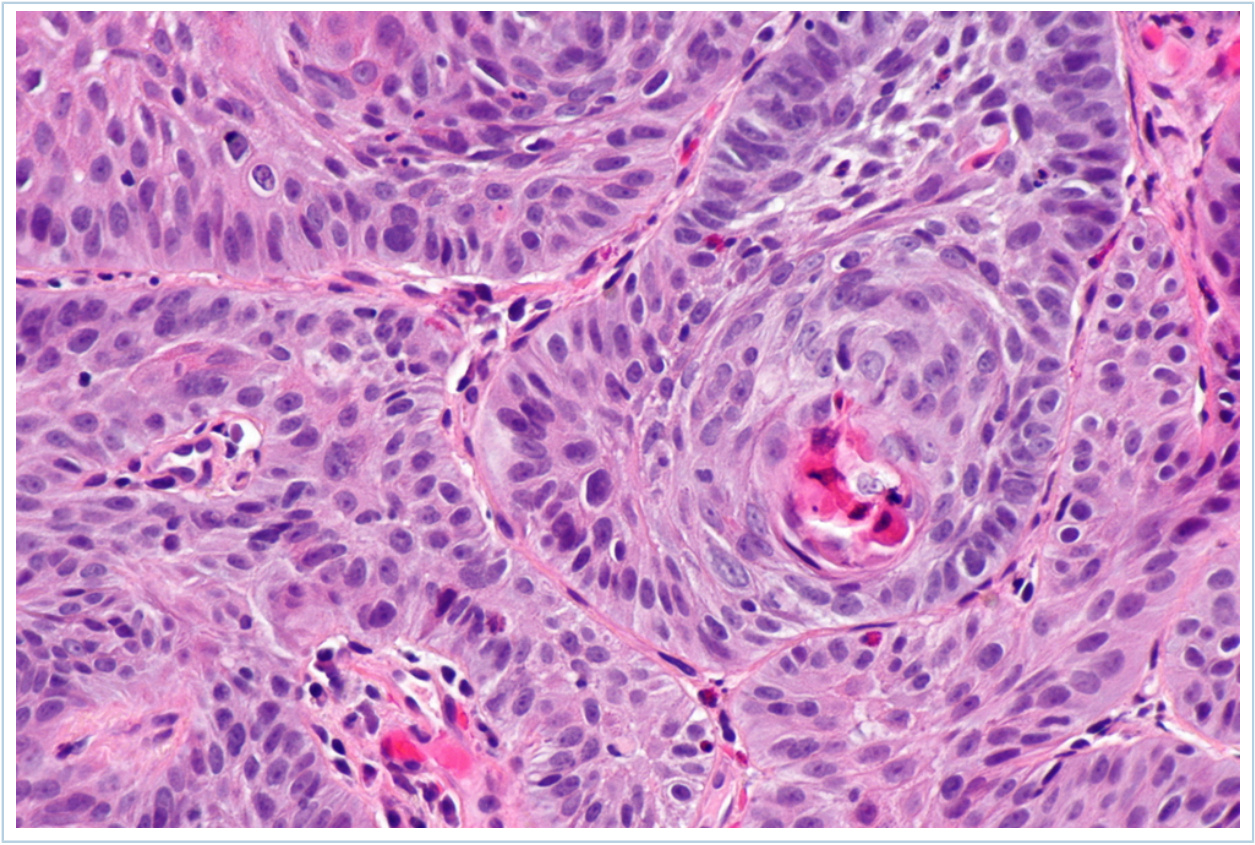
Molecular and pathological tests

Should be carried out at diagnosis to determine suitability for targeted therapies or immunotherapy.

All newly diagnosed patients should be tested for microsatellite instability (MSI) or mismatch repair deficiency (dMMR). Programmed death ligand 1 (PD-L1) testing is recommended in those with advanced or metastatic oesophageal cancers.

- Testing for MSI and dMMR is performed on formalin-fixed, paraffin-embedded (FFPE) tissue. MSI status is assessed by polymerase chain reaction (PCR) or next-generation sequencing (NGS) to measure gene expression levels of microsatellite markers (BAT25, BAT26, MONO27, NR21, NR24). MMR deficiency is evaluated by immunohistochemistry (IHC) to assess nuclear expression of proteins involved in DNA mismatch repair (MLH1, MSH2, MSH6, PMS2).[15] Results are interpreted as MSI-high (MSI-H) or MMR-deficient (dMMR) as per the College of American Pathologists (CAP) DNA mismatch repair biomarker reporting guidelines.[111]
- A qualitative IHC assay is used to detect PD-L1 protein levels in FFPE tumour tissue. The combined positive score (CPS) is used to evaluate if a specimen is considered to have PD-L1 expression. The CPS is determined by the number of PD-L1 stained cells (i.e., tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells evaluated, multiplied by 100. A CPS ≥1 indicates that a specimen has PD-L1 expression.[15] [112] An alternative is the tumour proportion score (TPS): this evaluates the percentage of viable tumour cells showing partial or complete membrane staining at any intensity (PD-L1 positivity is defined as TPS ≥1%).[88] TPS is only used in clinical-decision making for metastatic squamous cell carcinoma (based on CheckMate 648), whereas CPS is used in oesophageal and junctional adenocarcinoma and squamous cell carcinoma.[113]

All patients with inoperable locally advanced, recurrent, or metastatic EAC should should have human epidermal receptor 2 (HER2) status determined on diagnosis, as HER2-positive patients benefit from the addition of trastuzumab to first-line palliative chemotherapy.[15] [114] HER2-targeting is not routine practice in earlier disease settings, and consequently, establishing HER2 status would not impact clinical management outside the context of clinical trials. The reported rates of HER2 positivity in oesophageal cancers vary widely (2% to 45%) and are more frequently seen in adenocarcinoma (15% to 30%) than in squamous cell carcinoma (5% to 13%).[15]



Moderated differentiated, keratinising oesophageal carcinoma

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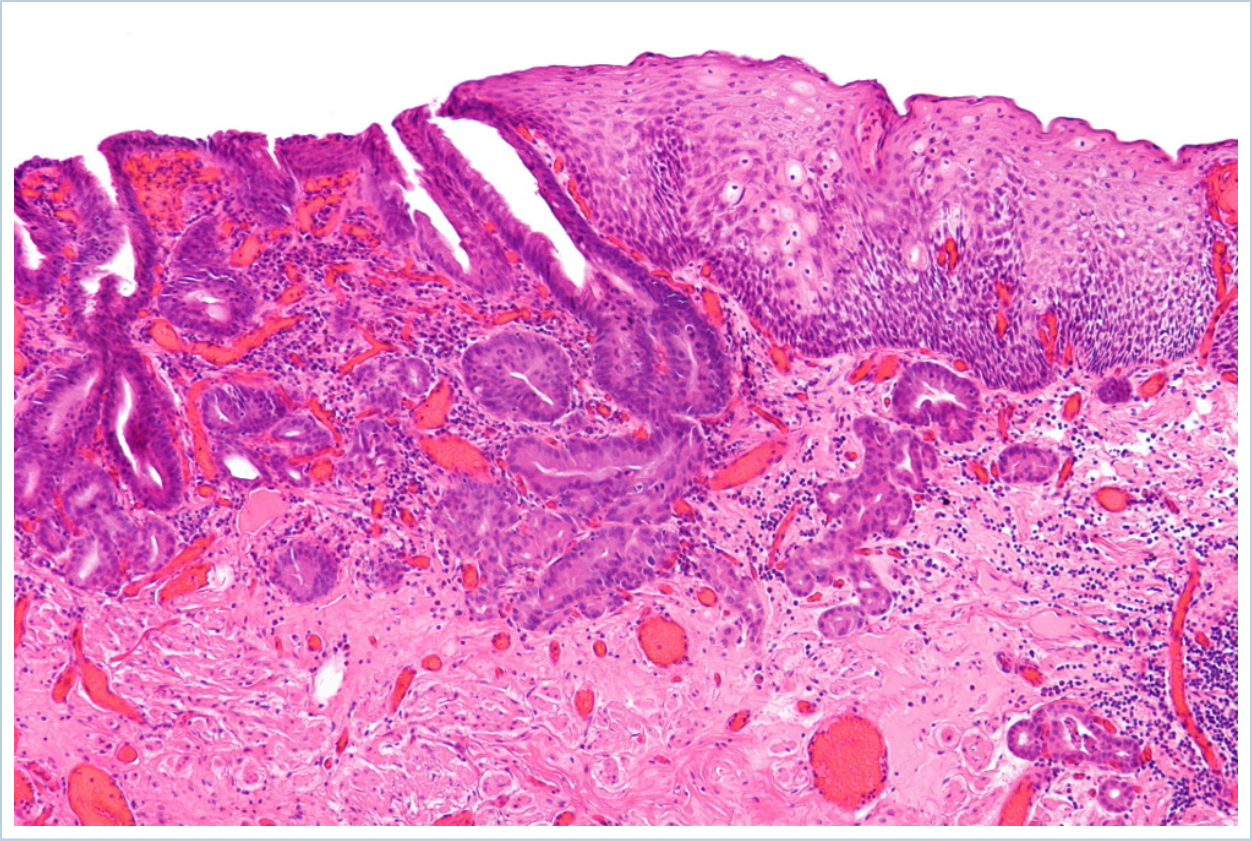


Adenocarcinoma (left of image) demonstrating glandular appearance with numerous mitotic cells and variable nuclear size and shape. Normal squamous epithelium is visible on the right of the image

Liquid biopsy

Liquid biopsy involves evaluating circulating tumour DNA by means of a blood test. It is used to detect mutations in DNA shed from oesophageal cancer, which can help to identify alterations that are targetable by available treatments. It is being used more frequently in patients with advanced or metastatic disease, especially those who are unable to undergo clinical biopsy for disease surveillance and management. A negative result does not exclude the presence of tumour mutations or amplifications and should therefore be interpreted with caution.[15]

Preoperative assessment

Management of locoregional oesophageal carcinoma often requires intensive therapy with a combination typically of induction chemoradiation (or chemotherapy alone) followed by surgery. However, many patients present with advanced disease and comorbidities that may affect the suitability of this treatment pathway.

Pulmonary function tests (PFTs) are crucial to determine the ability of the patient to withstand combined modality therapy. In patients with poor PFT results, a less invasive surgical approach, such as abdominocervical (transhiatal) oesophagectomy without thoracotomy, may be associated with lower morbidity and mortality.

Cardiac risk is assessed with cardiac stress testing and echocardiogram.

Nutritional status and history of weight loss should be assessed and nutritional support offered to all patients, in both curative and palliative settings. More than 50% of patients lose >5% of their body weight before admission for oesophagectomy, and 40% of patients lose >10%. Weight loss (independent of body mass index) is associated with increased operative risk, reduced quality of life, and poor survival in advanced disease.[88] The European Society for Medical Oncology (ESMO) recommends using European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines to aid assessment and management.[88] [115] Correction of malnutrition may be needed before curative-intent therapy can be started. While swallowing function generally improves after induction therapy, concerning levels of weight loss and malnutrition on presentation should be addressed early with enteral feeding, typically with placement of a gastrostomy or feeding jejunostomy tube.[88]

Exercise status should be asked about; reduced physical activity is associated with worse outcomes following perioperative treatment, and lower physical fitness is a negative predictor of long-term survival in oesophageal cancer. A supervised exercise programme has been shown to improve cardiorespiratory fitness and some aspects of quality of life in patients who have undergone oesophagectomy and is recommended in European guidelines.[88]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Important risk factors for oesophageal cancer include male sex; older age; tobacco use; excessive alcohol intake; Barrett's oesophagus; GORD; hiatus hernia; family history of oesophageal or other cancer; low socioeconomic status; non-white race; high-temperature beverages and foods; drinking maté; a diet low in fresh fruits and vegetables; and the presence of hereditary cancer syndromes.

dysphagia (common)

- The most common presenting symptom of oesophageal cancer.
- Dysphagia usually occurs only after there is obstruction of more than two-thirds of the lumen. Affected patients have generally progressed to locally advanced disease with at least T3 tumours and potentially nodal disease at the time of diagnosis.

odynophagia (common)

- Pain on swallowing is one of the signs of a locally advanced tumour, with possible invasion of the airway or mediastinum.

weight loss (common)

- One of the most common presenting signs. More than 50% of patients lose >5% of their body weight before admission for oesophagectomy, and 40% of patients lose >10%. Weight loss (independent of body mass index) is associated with increased operative risk, reduced quality of life, and poor survival in advanced disease.[88]
- When not associated with odynophagia or dysphagia, weight loss may be missed and contribute to a late presentation.
- European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines can be used to aid assessment and management of nutritional status.[115]

Other diagnostic factors

hiccups (uncommon)

- Phrenic nerve involvement can trigger hiccups.

postprandial/paroxysmal cough (uncommon)

- This may indicate the presence of an oesophagotracheal or oesophagobronchial fistula resulting from local invasion by a tumour.

Risk factors

Strong

male sex

- Male sex is a risk factor for both oesophageal squamous cell carcinoma and oesophageal adenocarcinoma.[20] [21] Approximately 70% of cases occur in men.[6][7]
- Between 2016 and 2020, the age-adjusted rate of new cases of oesophageal cancer in the US was 7.1 per 100,000 in men, and 1.7 per 100,000 in women.[7]
- The difference cannot be accounted for by other risk factors (e.g., gastro-oesophageal reflux disease, obesity), as these are equally divided between the sexes.[22]

older age

- The risk of oesophageal cancer increases with age, with peak incidence between 80 and 84 years.[19]

tobacco use

- Tobacco smoking strongly increases risk of oesophageal squamous cell carcinoma (OSCC) and moderately increases risk of oesophageal adenocarcinoma (OAC).[25]
- Current smokers have a ninefold increased risk of OSCC compared with non-smokers.[26] Smoking increases the risk of OAC and oesophago-gastric junction adenocarcinoma approximately two- to threefold.[26] [27]
- With respect to OSCC, there appears to be a synergistic effect in the presence of alcohol consumption.[44] [45]

excessive alcohol use (squamous cell carcinoma)

- Relative risk (RR) for oesophageal squamous cell carcinoma is increased for heavy drinkers compared with non-drinkers and occasional drinkers (RR 4.95, 95% CI 3.86 to 6.34).[43] There appears to be a synergistic effect in the presence of tobacco smoke.[44] [45]
- There is little evidence of an association between drinking alcohol and oesophageal adenocarcinoma.[69] [70]

Barrett's oesophagus (adenocarcinoma)

- Barrett's oesophagus (metaplasia of the mucosal lining of the distal oesophagus) is caused by long-standing gastro-oesophageal reflux. It is a pre-malignant condition for the development of oesophageal adenocarcinoma (OAC).[28]
- Risk of progression from Barrett's oesophagus to OAC is correlated with the degree of dysplasia present. The annual progression rate of low-grade dysplasia to high-grade dysplasia or OAC is 4%; the annual risk of progression from high-grade dysplasia to OAC is 25%.[30]

- A familial form of Barrett's oesophagus has been described, with multiple reports of familial clustering of patients with the condition. In a database analysis of patients diagnosed with Barrett's oesophagus or OAC in the Netherlands, 7% of cases were familial. These cases have a younger average age of onset of reflux symptoms and diagnosis of OAC than non-familial cases, suggesting a possible inherited predisposition to Barrett's oesophagus and/or OAC in some people.[31]

GORD (adenocarcinoma)

- One population-based case-control study found that people with gastro-oesophageal reflux disease (GORD) had a sevenfold increase in risk of developing oesophageal adenocarcinoma (OAC) compared with people without GORD.[32]
- More frequent, more severe, and longer-lasting symptoms were associated with a higher risk of cancer.[32]
- Use of theophyllines or anticholinergic medications to relax the lower oesophageal sphincter has been associated with modestly increased risk of OAC, although the association may be confounded by the presence of concomitant asthma or chronic obstructive lung disease.[33]

hiatus hernia (adenocarcinoma)

- The presence of a hiatus hernia increases risk of oesophageal adenocarcinoma twofold to sixfold, most probably by increasing gastro-oesophageal acid reflux.[25]

family history of oesophageal or other cancer (squamous cell carcinoma)

- In one population-based cohort-control study, cumulative risk of oesophageal cancer to age 75 was 12.2% among first-degree relatives of oesophageal squamous cell carcinoma (OSCC) cases and 7.0% in those of controls (hazard ratio [HR] 1.91, 95% CI 1.54 to 2.37).[54]
- Increased risk for OSCC has been associated with a family history of any cancer.[55]

low socioeconomic status

- A large number of epidemiological studies have confirmed that the risk of oesophageal cancer is higher in populations with lower socio-economic status (SES).[25]
- Various indicators of SES have been used in these studies, with most reporting an increased risk of two- to fourfold among those with lower SES compared with those who have higher SES.[25]

non-white race (squamous cell carcinoma)

- Incidence of oesophageal squamous cell carcinoma has been reported to be higher in non-white people.[16] [17]
- In the US, squamous cell carcinoma is more common than adenocarcinoma within the black population, with the incidence rate in black men being 4.5 times higher than that of white men.[10] [18]

high-temperature beverages and foods (squamous cell carcinoma)

- Habitual consumption of very hot drinks (as occurs in some cultures in Iran, China, Kenya, and elsewhere) has been associated with increased risk for oesophageal squamous cell carcinoma, by repeated thermal injury.[58] [59] [60] [61]

drinking maté (squamous cell carcinoma)

- Maté consumption is associated with an increased risk for oesophageal squamous cell carcinoma.[56] [57] Polycyclic aromatic hydrocarbons and thermal injury have been implicated.[25]

- Maté is an infusion of the herb *Ilex paraguayensis* (yerba maté). It is commonly consumed in southern Brazil, north-eastern Argentina, Uruguay, and Paraguay.[71] These areas also have the highest risks of oesophageal cancer in South America (mostly squamous cell).[72] [73]

low intake of fresh fruit and vegetables

- Evidence suggests that a high intake of fresh fruit and vegetables reduces the risk of oesophageal squamous cell carcinoma.[74] [75] [76]

hereditary cancer syndromes

- Tylosis (also known as focal non-epidermolytic palmoplantar keratoderma or Howel-Evans syndrome) is a rare autosomal dominant syndrome caused by germline mutations in the RHBDF2 gene. It is associated with an increased lifetime risk of developing oesophageal squamous cell carcinoma (OSCC), with an average age of diagnosis of 45 years. Routine screening by upper gastrointestinal endoscopy is recommended for patients and their family members starting from 20 years of age.[15]
- Bloom syndrome is a rare autosomal recessive disorder caused by a mutation in the BLM gene, which codes for the DNA repair enzyme RecQL3 helicase.[65] It is associated with an increased risk of developing multiple cancers, especially lymphoma and acute myeloid leukaemia, lower and upper gastrointestinal tract neoplasias (including OSCC), skin cancers, and cancers of the genitalia and urinary tract.[65] Screening for gastro-oesophageal reflux disease (with or without endoscopy to detect early oesophageal cancer) may be considered.[15]
- Fanconi anaemia (FA) is an autosomal recessive condition caused by germline mutations in any one of at least 21 genes associated with the FA pathway, which has a role in DNA repair. It presents with congenital abnormalities, progressive pancytopenia, and a predisposition to cancer (both haematological malignancies and solid organ tumours, particularly squamous cell carcinomas, including OSCC).[66] Upper gastrointestinal endoscopy may be considered as a screening strategy.[15]

Weak

obesity (adenocarcinoma)

- Elevated BMI is a risk factor for oesophageal adenocarcinoma (OAC), irrespective of the presence of gastro-oesophageal reflux disease.[34] [35] [36] [37]
- Case-control studies demonstrate a dose-dependent relationship between BMI and OAC.[37] [38]
- An inverse association between BMI and risk for oesophageal squamous cell carcinoma has been reported.[34] [36] [39] [40]

human papillomavirus (squamous cell carcinoma)

- Meta-analyses report an association between human papillomavirus (HPV) infection (serotypes 16 and 18) and incidence of oesophageal squamous cell carcinoma.[46] [47] [48] [49]
- An aetiological association between HPV infection and oesophageal cancer has not been demonstrated.[50] [51]

achalasia

- Achalasia is associated with an increased risk for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma.[23] [24]

vitamin and mineral deficiencies (squamous cell carcinoma)

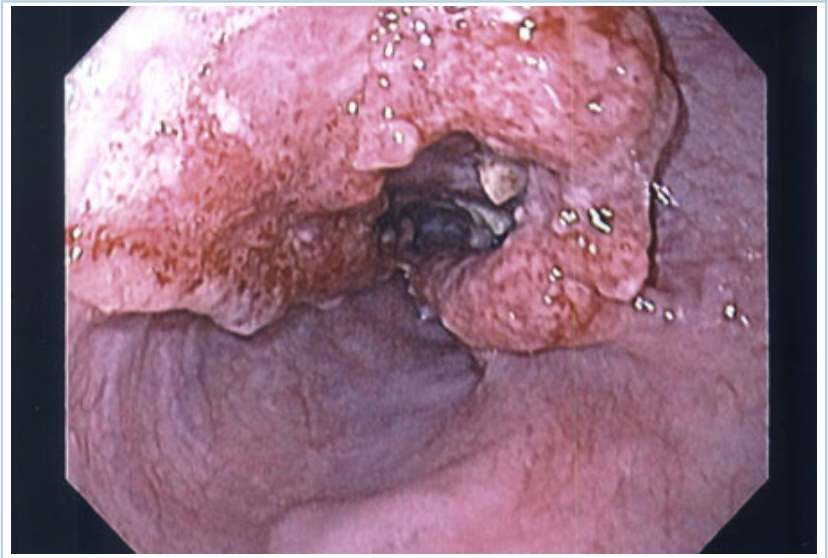
- Vitamin and mineral deficiencies may contribute to increased risk for oesophageal cancer in some regions.[52] [53]
- Antioxidant supplements have not been consistently demonstrated to reduce the risk of oesophageal cancer.[77] [78] [79]

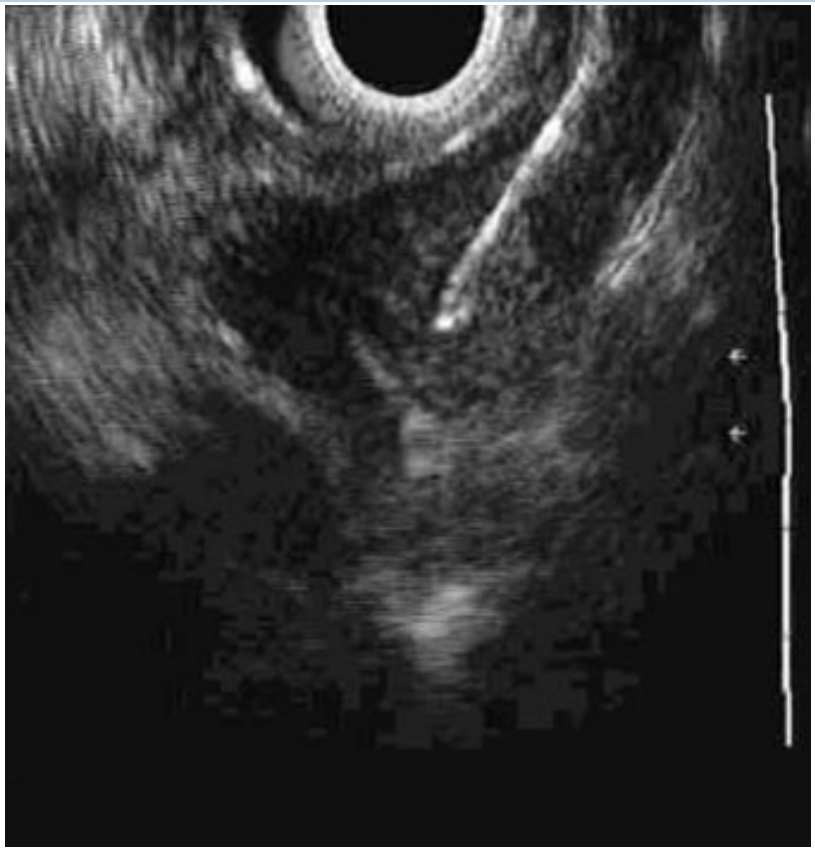
poor oral hygiene (squamous cell carcinoma)

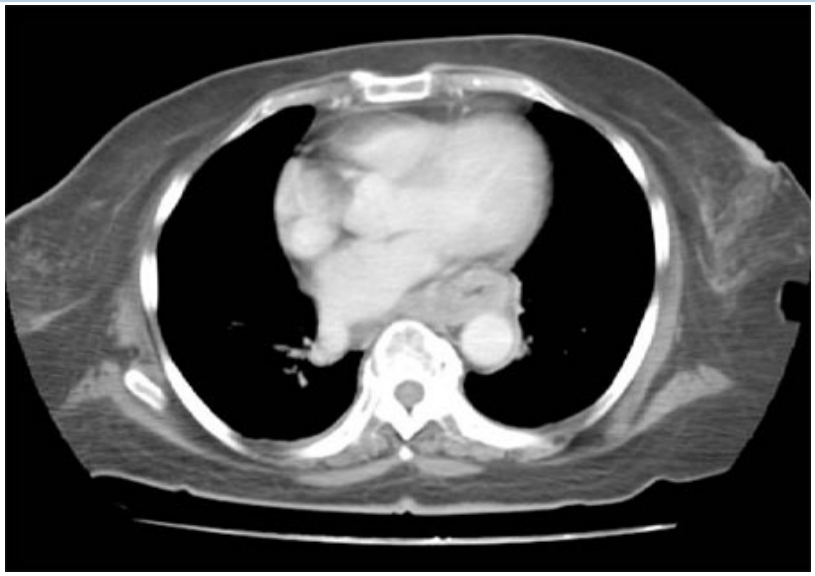
- Case-control studies have demonstrated an association between oesophageal squamous cell carcinoma and poor oral hygiene, irrespective of alcohol and tobacco use.[62] [63] [64]

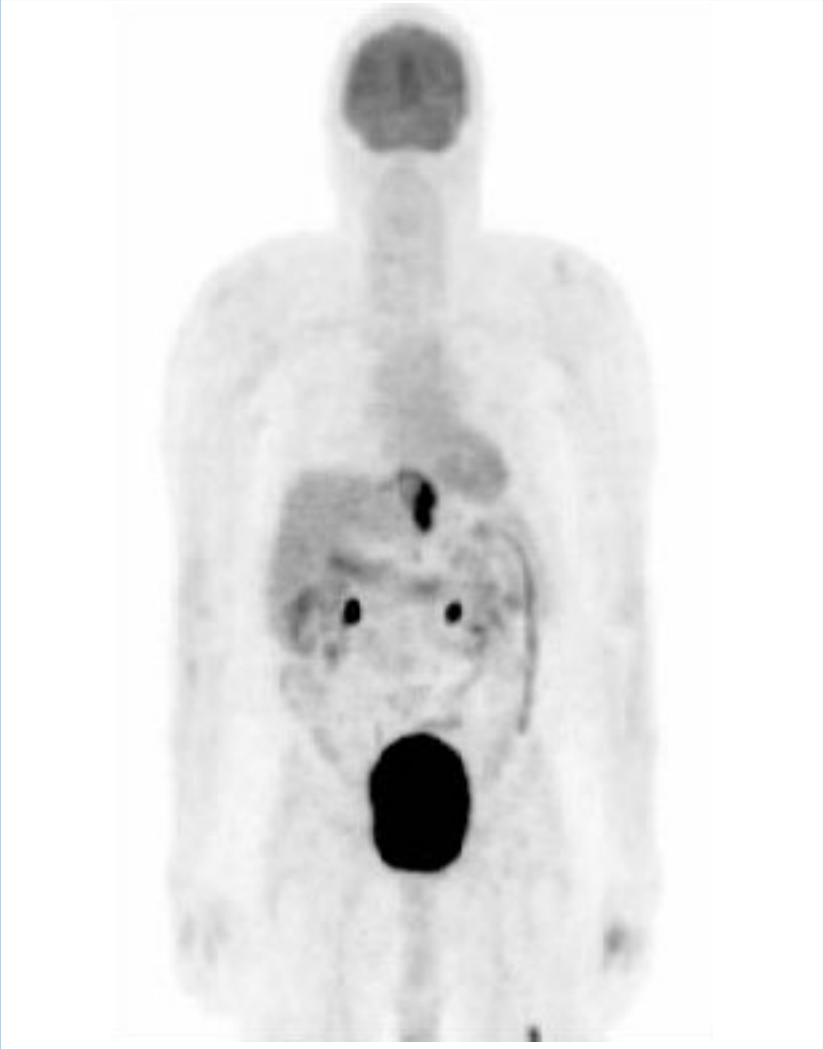
Investigations

1st test to order

Test	Result
oesophagogastroduodenoscopy (OGD) with biopsy • OGD is the first test in patients with severe dysphagia, odynophagia, or weight loss.[88] This will differentiate oesophageal cancer from benign causes of dysphagia.  *Endoscopic view of oesophageal cancer* *Personal collection of Mark J. Krasna* • Confocal laser endoscopy with targeted biopsy can improve the diagnostic yield for neoplasia and decrease the number of mucosal biopsies in patients undergoing surveillance.[116] [117] [118]	**mucosal lesion; histology shows squamous cell carcinoma or adenocarcinoma**
endoscopic ultrasound (EUS) ± fine needle aspiration (FNA) • Should be performed before treatment for initial clinical staging of the cancer.[15] EUS can identify all the histological layers of the oesophagus and thereby confirm the T stage. The sensitivity and specificity of EUS for staging oesophageal cancer has been reported to be: 81.6% and 99.4% in T1 tumours; 81.4% and 96.3% in T2 tumours; 91.4% and 94.4% in T3 tumours; and 92.4% and 97.4% in T4 tumours, respectively.[102] • EUS can identify abnormal or enlarged mediastinal and celiac axis lymph nodes, and enable cytological examination by FNA. The overall accuracy of EUS/FNA for locoregional staging of oesophageal cancer prior to therapy is 87%; the comparable figure for EUS alone is 74%.[100] [101]	**indicates extent of local invasion and presence or absence of spread to lymph nodes**

Test	Result
 *Endoscopic ultrasound-guided fine needle aspiration of lymph node* *Personal collection of Mark J. Krasna* • Complications of EUS (with or without FNA) include perforation (0.02% to 0.08%), haemorrhage (0.13% to 0.69%), and infection (0.4% to 1.7%).[107]	
CT thorax and abdomen • CT scan of the chest and abdomen is often performed if the suspicion of oesophageal cancer is high or biopsy confirms the diagnosis.[89] • CT is most helpful to assess tumour bulk and visceral metastases. • CT can also help identify the thickness of the oesophageal lesion and presence of spread to lymph nodes.	**indicates size of primary tumour, local invasion, and presence or absence of metastases**

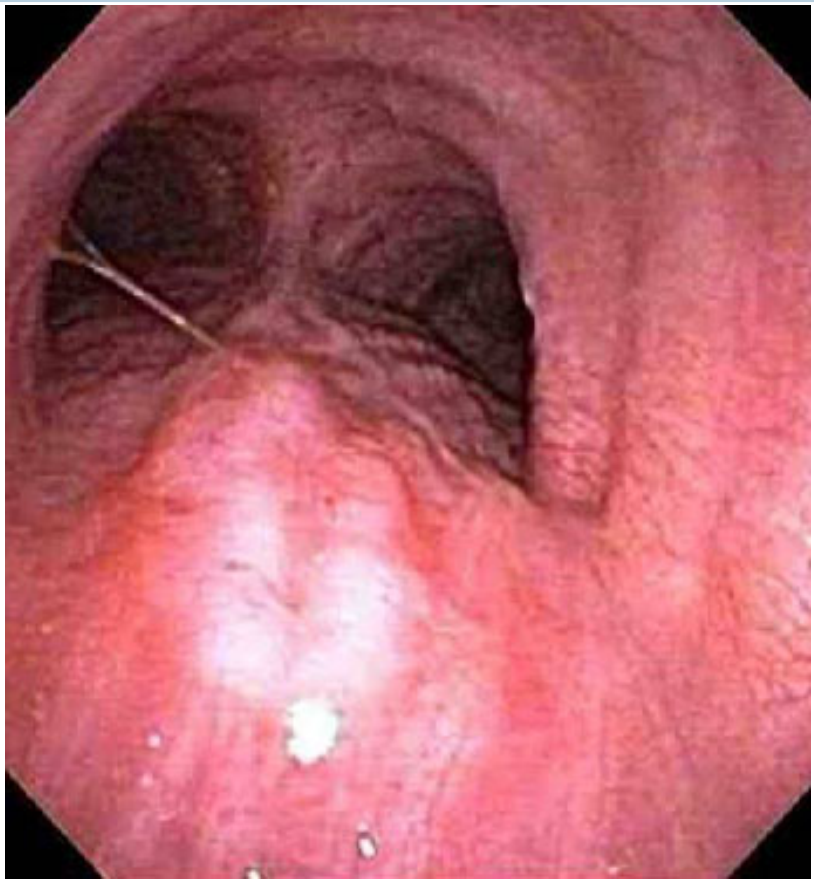
Test	Result
 *CT scan showing T3 tumour at level of inferior pulmonary vein* *Personal collection of Mark J. Krasna* • Oral and intravenous contrast should be used to ensure optimal opacification of the lumen and visualisation of the heart, mediastinal vessels, and liver.[89]	
(18F)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan • Improves the accuracy of staging and facilitates selection of patients for surgery, by detecting distant metastatic disease not identified by CT alone.[89]	**hyperactivity (hot spot) at primary tumour site and locoregional disease; may also show activity in lungs, liver, or bones suggestive of metastases**

Test	Result
 *PET scan showing oesophageal cancer at the gastro-oesophageal junction. Note metastatic deposit in left femur* *Personal collection of Mark J. Krasna* • PET can be used to detect responses to chemotherapy and radiotherapy.[94] [95] [96] In patients with oesophageal cancer, relative changes in FDG uptake can predict response to neoadjuvant therapy.[97] [98] • An FDG-PET scan is generally done before endoscopic ultrasound (EUS) to avoid unnecessary testing in patients with metastatic disease.[99]	
molecular and pathological tests • Should be carried out at diagnosis to determine suitability for targeted therapies or immunotherapy. Testing is carried out on tumour tissue obtained at biopsy. • Microsatellite instability (MSI) and/or mismatch repair (MMR) testing • All newly diagnosed patients should be tested for MSI or mismatch repair deficiency (dMMR). Programmed death ligand 1 (PD-L1) testing is recommended in those with advanced or metastatic oesophageal cancers. • Testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue. MSI status is assessed by polymerase chain reaction (PCR) or next-generation sequencing (NGS) to measure gene expression levels of microsatellite markers (BAT25, BAT26, MONO27, NR21,	**HER2-positive or HER2-negative; MSI-high (MSI-H) or MSI-low (MSI-L) or MSI-stable (MSS); MMR-deficient (dMMR) or no evidence of deficient mismatch repair; PD-L1 expression: positive (CPS ≥1 or TPS ≥1%) or negative (CPS <1 or TPS <1%)**

Test	Result
NR24). MMR deficiency is evaluated by immunohistochemistry (IHC) to assess nuclear expression of proteins involved in DNA mismatch repair (MLH1, MSH2, MSH6, PMS2).[15] Results are interpreted as MSI-high (MSI-H) or MMR-deficient (dMMR, deficient mismatch repair) as per the College of American Pathologists (CAP) DNA mismatch repair biomarker reporting guidelines.[111] • Human epidermal receptor 2 (HER2) status • All patients with locally advanced, recurrent, or metastatic inoperable oesophageal adenocarcinoma should have HER2 status determined on diagnosis, as HER2-positive patients benefit from the addition of trastuzumab to first-line palliative chemotherapy.[15] [114] HER2-targeting is not routine practice in earlier disease settings, and consequently, establishing HER2 status would not impact clinical management outside the context of clinical trials. • HER2 status is assessed using immunohistochemistry (IHC) ± in-situ hybridisation (ISH). An alternative is next-generation sequencing (NGS), which offers the opportunity to assess numerous mutations simultaneously.[15] • The reported rates of HER2 positivity in oesophageal cancers vary widely (2% to 45%) and are more frequently seen in adenocarcinoma (15% to 30%) than in squamous cell carcinoma (5% to 13%).[15] • Programmed death-ligand 1 (PD-L1) testing • May be considered on locally advanced, recurrent, or metastatic oesophageal and oesophagogastric junction cancers in patients who are candidates for treatment with PD-1 inhibitors. A qualitative IHC assay is used to detect PD-L1 protein levels in FFPE tumour tissue. • The combined positive score (CPS) is used to evaluate if a specimen is considered to have PD-L1 expression. The CPS is determined by the number of PD-L1 stained cells (i.e., tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells evaluated, multiplied by 100. A CPS ≥1 indicates that a specimen has PD-L1 expression.[15] [112] An alternative is the tumour proportion score (TPS): this evaluates the percentage of viable tumour cells showing partial or complete membrane staining at any intensity (PD-L1 positivity is defined as TPS ≥1%).[88] TPS is only used in clinical-decision making for metastatic squamous cell carcinoma (based on CheckMate 648), whereas CPS is used in oesophageal and junctional adenocarcinoma and squamous cell carcinoma.[113]	

Other tests to consider

Test	Result
comprehensive metabolic profile • Should be performed in advanced cases with near or complete oesophageal obstruction. These patients may become severely volume-depleted and hypokalaemic because of their inability to swallow fluids and their own potassium-rich saliva.	**advanced cases: hypokalaemia, elevated creatinine and serum urea/nitrogen**
MRI thorax and abdomen • An alternative to CT for the staging of oesophageal cancer, particularly in detecting metastatic disease to visceral organs. • Highly accurate when assessing the liver or adrenals and for determining advanced local spread (T4). • Less reliable in defining early infiltration (T1 to T3). • Appears to be sensitive in predicting mediastinal invasion; the loss of signal in the vessels and the air-filled trachea and bronchi may provide a clear delineation between the tumour and the aorta and the tracheobronchial tree. • Like CT scans, MRI scans are poor at detecting tumours restricted to mucosa or submucosa, and also tend to under-stage the regional lymph nodes.[92]	**indicates size of primary tumour, local invasion, and presence or absence of metastases**
bronchoscopy ± fine needle aspiration (FNA) • In patients with disease of the middle and upper thirds of the oesophagus, bronchoscopy with FNA can be helpful in determining involvement of the tracheobronchial tree. Bronchoscopy should be performed prior to considering surgery on tumours at these locations. • FNA can be performed into mucosal lesions within the lumen, or transbronchially into lesions adjacent to the airway.	**normal or may show involvement of tracheobronchial tree**

Test	Result
 *Tracheal invasion (T4) confirmed by bronchoscopy* *Personal collection of Mark J. Krasna*	
thoracoscopy and laparoscopy • May be appropriate in selected patients; for example, those with adenocarcinoma of the oesophagus or oesophago-gastric junction with significant extension into the cardia.[108] Studies indicate that thoracoscopy and laparoscopy may improve accuracy compared with non-invasive testing in these situations.[109] [110]	**may reveal metastatic disease**
liquid biopsy • Involves evaluating circulating tumour DNA (ctDNA) by means of a blood test. It is used to detect mutations in DNA shed from oesophageal cancer, which can help to identify alterations that are targetable by available treatments. It is being used more frequently in patients with advanced or metastatic disease, especially those who are unable to have a clinical biopsy for disease surveillance and management. A negative result does not exclude the presence of tumour mutations or amplifications and should therefore be interpreted with caution.[15]	**ctDNA-positive or negative**
pulmonary function tests • Crucial to determine the ability of the patient to withstand combined modality therapy. In patients with poor pulmonary function test results, a less invasive surgical approach, such as transhiatal oesophagectomy without thoracotomy, may be associated with lower morbidity and mortality.	**normal or reduced**

Test	Result
cardiac stress test • Helpful to identify underlying cardiac abnormalities prior to surgery.	**normal or may show cardiac abnormality**
echocardiogram • Helpful to identify underlying cardiac abnormalities prior to surgery.	**normal or may show cardiac abnormality**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Benign stricture	• Usually associated with a long history of heartburn and slowly progressive dysphagia.	• Oesophagogastroduodenoscopy (OGD) shows stricture of benign aetiology.
Achalasia	• Long history of regurgitation with no history of heartburn. May be clinically indistinguishable from oesophageal cancer.	• Upper gastrointestinal series shows a typical 'bird's beak' filling defect. • Caution is required to differentiate achalasia from pseudoachalasia (which is caused by a primary or secondary malignancy in the majority of patients). It is crucial therefore to follow up with an endoscopy for mucosal assessment and biopsy. • OGD has low sensitivity for the diagnosis of achalasia, and is often reported to be normal in early achalasia. • Oesophageal manometry shows incomplete relaxation of the lower oesophageal sphincter.
Barrett's oesophagus	• Long-standing reflux. Dysphagia is rare.	• OGD and biopsy will differentiate between benign intestinal metaplasia, dysplasia, and actual invasive cancer.

Criteria

American Joint Committee on Cancer TNM staging system (8th edition)[119]

The American Joint Committee on Cancer (AJCC) staging system describes the extent of disease based on the following anatomical factors: size and extent of the primary tumour (T); regional lymph node involvement (N); and presence or absence of distant metastases (M).

Non-anatomical prognostic factors (e.g., tumour grade, signet ring cell histology, biomarkers) may be used to supplement the staging of certain cancers.

Paris classification - submucosal (SM) staging[120] [121] [122]

Assessment of depth of submucosal invasion following endoscopic resection is important as it is strongly associated with the risk of lymph node metastases.[123] The submucosa can be divided into thirds (SM1/SM2/SM3). Measurement of the depth of invasion below the original muscularis mucosae is used to determine SM staging. The most commonly used staging system for oesophageal adenocarcinoma proposes the following cut-offs:[120]

- SM1: >0 to ≤500 micrometres
- SM2 - SM3: >500 micrometres

For squamous cell carcinoma, a cut-off of 200 micrometres for SM1 has been suggested.[124]

Screening

In high-incidence areas, such as Guangdong province in China, there is evidence that cytological or endoscopic screening is appropriate and helpful. Research is ongoing.[125]

In patients with Barrett's oesophagus, continued surveillance is indicated to identify pre-malignant lesions (high-grade dysplasia) and early carcinoma in situ. Guidelines recommend screening and surveillance intervals for patients with Barrett's oesophagus.[126] [127] [128] [129] Ablation of dysplastic Barrett's oesophagus has been demonstrated to reduce the progression to invasive malignancy.[130]

Approach

Treatment for oesophageal cancer is complex and depends on multiple factors, including disease stage, histology (squamous cell carcinoma or adenocarcinoma), tumour location, biomarker status (e.g., human epidermal receptor 2 [HER2]; metastatic microsatellite instability-high [MSI-H]; mismatch repair deficient [dMMR]; and programmed death-ligand 1 [PD-L1]), performance status, comorbidities, and patient preference.[88]

Initial treatment options include the following (some can be combined in certain patients):

- Endoscopic therapy
- Surgery (oesophagectomy)
- Radiotherapy
- Chemotherapy
- Chemoradiotherapy
- Targeted therapy
- Palliative/supportive care

The initial treatment approach is typically guided by clinical disease stage (i.e., limited [cT1, cN0, M0], localised [cT2, cN0, M0], locally advanced [cT3-4 or cN1-3, M0)], or metastatic [M1]), histology subtype, and suitability for surgery.

All patients require careful treatment planning that involves a multidisciplinary team (e.g., surgical oncology, medical oncology, radiation oncology, radiology, gastroenterology, pathology). Patients with locally advanced, metastatic, or recurrent disease may require a combination of local and systemic treatments (i.e., multimodality treatment).[131]

Endoscopic therapy

Endoscopic therapy includes endoscopic resection (using endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD]) and/or endoscopic ablation (using cryoablation or radiofrequency ablation). Endoscopic resection is recommended for the accurate staging of early-stage cancers (T1a or T1b based on endoscopic ultrasound [EUS]).[15]

Endoscopic therapy is considered to be a safe and effective treatment option for patients with limited (cT1) disease. Specifically, patients with T1a disease, superficial T1b tumours, and those lacking poor differentiation or lymphovascular invasion are candidates for endoscopic resection for curative intent. Procedures should be performed at a specialised centre with appropriate expertise in gastrointestinal endoscopy, imaging, surgery, and pathology.[88] [132] [133] Endoscopic treatments can also be used in palliative care. Dilating balloons or bougies can be inserted for temporary relief from tumour obstruction or strictures, and dysphagia can be relieved by endoscopic tumour ablation or placement of self-expanding metal stents. Endoscopy can also be used to assist with the placement of feeding gastrostomy or jejunostomy tubes in the palliation of patients with anorexia, dysphagia, or malnutrition.[15]

EMR and ESD

EMR involves the use of an endoscopic snare device to resect lesions. In contrast, ESD involves dissecting lesions from the submucosa layer, followed by en bloc resection of the dissected lesions.[134]

EMR may be less time-consuming, and associated with a lower risk of severe adverse events, than ESD. However, its use is limited to smaller lesions.

For larger lesions, ESD is recommended.[122] [135] ESD has been found to be associated with higher curative resection rates and lower local recurrence rates compared with EMR, particularly for large (≥20 mm) squamous cell carcinoma lesions.[122] [135]

ESD is more useful than EMR for assessing lesion size, submucosa invasion, differentiation, and lymphovascular invasion. However, it is more time-consuming to perform and is associated with a higher risk of complications (e.g., bleeding, perforation) compared with EMR.[134] [136] [137]

The American Society for Gastrointestinal Endoscopy (ASGE) suggests selecting resection strategy on the basis of lesion size in patients with oesophageal squamous cell dysplasia or early, well-differentiated, non-ulcerated squamous cell carcinoma. Either ESD or EMR can be used when lesion size is ≤15 mm, while ESD is preferred over EMR when lesion size is >15 mm.[138] Further, in patients with early, well-differentiated, non-ulcerated Oesophageal adenocarcinoma (T1 stage) or nodular Barrett's dysplasia, the ASGE suggests using either ESD or EMR when lesion size is ≤20 mm, while ESD is preferred over EMR when lesion size is >20 mm.[138]

Endoscopic ablation

Involves thermal injury through heat (burning, coagulation necrosis) or freezing (cryotherapy) to destroy, rather than remove, neoplastic tissue.[139] Endoscopic ablation does not facilitate further diagnostic evaluation, but it is usually performed following EMR or ESD, after the resection site has healed, to help completely eliminate any residual dysplasia or treat non-dysplastic Barrett's oesophagus.[15]

Pathological staging and histological diagnosis

EMR and ESD facilitate pathological staging and histological diagnosis. This is particularly useful for staging patients with limited disease because clinical staging (using computed tomography or magnetic resonance imaging) cannot accurately differentiate T1a disease (no submucosa involvement) and T1b disease (with submucosa involvement).[91]

Endoscopic resected specimens obtained during EMR and ESD should be sent for histopathology assessment to determine pathological stage and, importantly, depth of submucosal invasion. Depth of submucosal invasion is strongly associated with risk of lymph node metastases.[123] Additionally, deep margin status is important to determine if endoscopic therapy alone may be curative.

Surveillance

EUS has a high sensitivity for detecting recurrent disease post treatment. EUS-guided fine needle aspiration biopsy (EUS-FNA) should be undertaken if abnormalities are detected on cross-sectional imaging (e.g., suspicious lymph nodes or areas of wall thickening).[15]

Surgery (oesophagectomy)

Surgery is the cornerstone of treatment for oesophageal cancer. Surgery is usually carried out with curative intent. The main surgical approaches are:

- Transthoracic oesophagectomy (Ivor Lewis or Mckeown procedures)
- Transhiatal oesophagectomy

Transthoracic oesophagectomy is often preferred because it allows direct visualisation of the thoracic oesophagus with extensive lymphadenectomy. Some data suggest improved survival compared with transhiatal oesophagectomy in patients with resectable oesophageal adenocarcinoma. However,

historically, the morbidity of complications following Ivor Lewis oesophagectomy (e.g., intrathoracic anastomotic leak) has led some surgeons to favour a cervical anastomosis via either McKeown or transhiatal approaches. With improved endoscopic options such as stent and endoluminal vacuum sponges, the morbidity of an intrathoracic leak may be reduced when managed at experienced centres.

In transthoracic oesophagectomy, gastric tube reconstruction is performed with either an intrathoracic anastomosis (Ivor Lewis) or a cervical anastomosis (McKeown).[140] The Ivor Lewis procedure is most appropriate for distal thoracic lesions, whereas the McKeown procedure can be used for tumours more proximally in the oesophagus (e.g., middle-third).[15]

A transhiatal oesophagectomy involves a laparotomy and left cervical incision. It can be used for lesions at any thoracic location; however, transhiatal dissection of large middle-oesophageal tumours adjacent to the trachea is difficult and may be associated with considerable risk.[15] European guidelines suggest a role for transhiatal oesophagectomy in patients where morbidity from a thoracotomy incision may be considered excessive.[88]

The type of resection is dictated by the tumour location, and choices available for conduit, as well as the surgeon's experience and preference, whilst taking the patient's preference into consideration.[15]

Surgery should be carried out at high-volume centres and by surgeons experienced in performing oesophagectomy.[15] Studies have found that high-volume centres have a lower mortality rate compared with low-volume centres.[141] There is also evidence to suggest that surgeon volume is a stronger prognostic factor than hospital volume.[141] [142]

Minimally invasive surgery

Minimally invasive surgery involves performing oesophagectomy under thoracoscopic and laparoscopic visualisation. Minimally invasive surgery has been shown to have comparable outcomes to open oesophagectomy for benign and non-locally advanced cancer.[143] In experienced centres, it is recommended as the surgical approach of choice.[88]

Techniques involve minimally invasive Ivor Lewis (laparoscopy and limited right thoracotomy) or McKeown (right thoracoscopy, limited laparotomy/laparoscopy, and cervical anastomosis) oesophagectomies. However, hybrid techniques, which combine either thoracoscopy or laparoscopy with open surgery (for the abdominal or the thoracic component of the procedure, respectively), have also been described as minimally invasive.[144]

Laparoscopic and thoracoscopic or robotic-assisted minimally invasive oesophagectomy offers benefits in terms of decreased perioperative pulmonary complications and postoperative complications, faster recovery, and improved short-term quality of life.[145] [146] [147]

Randomised studies demonstrate that, compared with standard transthoracic oesophagectomy, both minimally-invasive transthoracic oesophagectomy and hybrid minimally invasive oesophagectomy (an Ivor Lewis procedure with laparoscopic gastric mobilisation and limited open right thoracotomy) lead to significantly lower rates of postoperative complications and accelerated recovery, without compromising survival benefit.[148] [149]

Radiotherapy

Radiotherapy (preoperative, postoperative, or palliative) can be used for both oesophageal and oesophago-gastric junction tumours. Most patients should receive radiotherapy in combination with

chemotherapy (chemoradiotherapy) due to significantly better outcomes than with radiotherapy alone; radiotherapy as a sole treatment should generally be reserved for palliation or for patients who are unable to receive chemotherapy.[15]

Treatment for Siewert Type 1 and 2 tumours generally follows guidelines for oesophageal and oesophago-gastric tumours, whereas treatment for Siewert Type 3 tumours usually follows guidelines for radiotherapy of gastric cancer.[15]

Recommendations may be adapted according to location and bulk of the tumour.[15] A dose range of 41.4 to 50.4 Gy is recommended for preoperative therapy, and 45 to 50.4 Gy for postoperative therapy. Non-surgical candidates can receive doses of 50 to 50.4 Gy.[15]

Chemotherapy

Preoperative and perioperative chemotherapy should only be used for adenocarcinoma of the thoracic oesophagus or oesophago-gastric junction.[15]

The value of postoperative chemotherapy remains uncertain.

Chemoradiotherapy

Preoperative chemoradiation with paclitaxel and carboplatin plus radiotherapy is the preferred approach for localised resectable disease.[15] [150] One Cochrane review found that preoperative chemotherapy followed by oesophagectomy improved survival compared with surgery alone in patients with resectable thoracic oesophageal cancer.[151] [Evidence B] Definitive chemoradiotherapy should be reserved for those who have unresectable disease, decline surgery, or have prohibitive surgical risk.[15] [152] [153]

Patients undergoing upfront surgery for presumed limited disease found to have node positive on final pathology should be considered for adjuvant chemoradiation if poor nodal harvest was achieved and there is concern for suboptimal surgery.[15]

Targeted therapy

It is important that all patients with oesophageal cancer undergo biomarker testing (e.g., for HER2, MSI-H, dMMR, and PD-L1 overexpression) to identify those suitable for targeted therapies.These agents may be used alone or in combination with chemotherapy, depending on the drug. Available preferred options recommended for unresectable locally advanced, recurrent, or metastatic disease include trastuzumab, nivolumab, and pembrolizumab. The preferred treatment options for MSI-H/dMMR tumours include pembrolizumab (alone or in combination with fluoropyrimidine- and platinum-based chemotherapy), dostarlimab, and nivolumab (in combination with ipilimumab or fluoropyrimidine- and platinum-based chemotherapy).

Trastuzumab (an anti-HER2 monoclonal antibody) is approved for use in patients with previously untreated metastatic HER2-positive adenocarcinoma, in combination with first-line platinum- and fluoropyrimidine-based chemotherapy.[15] [114] [154] In the ToGA trial, trastuzumab combined with chemotherapy (cisplatin plus either capecitabine or fluorouracil) improved survival (16.0 vs. 11.8 months) in patients with HER2-positive oesophageal and gastric adenocarcinoma compared with chemotherapy alone.[114]

In the US, pembrolizumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line therapy with a fluoropyrimidine, a platinum agent, and trastuzumab for patients with HER2-positive adenocarcinoma.[15] [155] Pembrolizumab plus fluoropyrimidine- and platinum-based

chemotherapy may be used for the first-line treatment of patients with squamous cell carcinoma or HER2-negative adenocarcinoma.[15] [88] [155] In Europe, this approval is limited to patients with combined positive score (CPS) ≥10. In the KEYNOTE-859 study comprising patients with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma, the combination of pembrolizumab with chemotherapy has shown significant and clinically meaningful improvement in overall survival with manageable toxicity, compared with placebo.[156]

Nivolumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line treatment with fluoropyrimidine- and platinum-based chemotherapy for patients with HER2-negative advanced oesophageal or oesophagogastric junction adenocarcinoma.[15] [155] The National Institute for Health and Care Excellence (NICE) in the UK recommends nivolumab after fluoropyrimidine and platinum-based therapy for the treatment of previously treated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma in adults.[157] NICE further recommends nivolumab plus fluoropyrimidine-based and platinum-based therapy as an option in adults with untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 at a level of 1% or more when pembrolizumab plus chemotherapy is not found to be suitable.[158] Nivolumab is approved in combination with fluoropyrimidine- and platinum-based chemotherapy and in combination with ipilimumab for the first-line treatment of patients with advanced oesophageal squamous cell carcinoma (ESCC).[15] [155]

Dostarlimab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) is approved for the treatment of patients with DNA mismatch repair-deficiency recurrent or advanced solid tumours that have progressed on or following prior treatment, who have no alternative treatment options, and who have not previously received a PD-1 or PD-L1 inhibitor.[15] The non-randomised phase-1 multi-cohort GARNET trial evaluated the safety and efficacy of dostarlimab in 209 patients with dMMR solid tumours (the majority of which were endometrial or gastrointestinal cancers) who had not received previous PD-1 or PD-L1 inhibitors. At 12 months of follow-up the overall response rate was 38.7%, with a 7.5% complete response rate.[159]

Palliative/supportive care

The focus of palliative/supportive care should be to prevent and relieve suffering primarily due to dysphagia, obstruction, pain, bleeding, and nausea and vomiting.[15] Early palliative care referral and nutritional support should be offered.[88]

Photodynamic therapy (PDT) involves the activation of an exogenously administered, or an endogenously generated, photosensitiser with light to produce localised tissue destruction.[160] Palliative laser and PDT for oesophageal obstruction has been associated with stricture formation.[161] [162] [163]

Cryotherapy (using liquid nitrogen) is under investigation for the treatment of squamous dysplasia of the oesophagus (especially in patients who are high-risk for surgery).[164] [165]

Insertion of self-expanding metal stents combined with brachytherapy provides comparable palliative relief of dysphagia to endoscopic ablation techniques.[166] It is associated with a reduced requirement for re-interventions. Various other techniques, including rigid plastic tube insertion, dilation alone or in combination with other therapies, chemotherapy or chemoradiotherapy, and bypass surgery, are associated with a high rate of delayed complications and recurrence of dysphagia.[166]

Limited disease (cT1, cN0, M0)

Endoscopic therapy (EMR or ESD, with or without endoscopic ablation) or surgery (oesophagectomy) are the recommended initial treatment options for patients with limited disease (both squamous cell carcinoma and adenocarcinoma).[15] [88] [133] [167] The goal of treatment is complete disease eradication and cure.

T1a disease

Endoscopic therapy alone is recommended for most patients with cT1a disease (i.e., disease limited to the lamina propria and muscularis mucosae).[15] [88] No further surgical treatment is required. Endoscopic resection can usually be considered curative in all T1a adenocarcinomas.[88] Oesophageal squamous cell carcinomas (OSCC) have a higher risk of lymph node metastasis and features such as differentiation and lymphovascular invasion should be considered. Esophagectomy is indicated for patients with extensive T1a ESCC, particularly nodular disease that is not controlled with endoscopic therapy.[15] [88]

In a SEER database analysis of 1458 patients with T1N0 oesophageal cancer, the overall survival rates were similar after treatment with surgery or endoscopic therapy, but those treated with endoscopic therapy had improved cancer-specific survival and decreased morbidity.[168]

Residual Barrett's oesophagus should be ablated following endoscopic therapy to minimise the risk of subsequent cancer.[15] [88] Following endoscopic therapy, patients require continuous monitoring with routine interval endoscopies.

T1b disease

Oesophagectomy is recommended for patients with cT1b disease (squamous cell carcinoma or adenocarcinoma) who are suitable for surgery.[15] [88] [133] [169] [170]

Patients with superficial T1b adenocarcinomas may be considered for initial treatment with endoscopic therapy instead of surgery.[88] If histopathological assessment of endoscopic resected specimens confirms superficial T1b disease (i.e., submucosa invasion <500 micrometres), no ulceration, and the presence of low-risk lesions (i.e., no lymphovascular invasion, well-differentiated histology, negative margins) then no further surgical treatment is required. The ASGE suggests that patients with oesophageal squamous cell dysplasia or early, well-differentiated, non-ulcerated ESCC who do not show overt signs of submucosal invasion need not undergo surgical resection.[138] Surgery is required if histopathological assessment confirms deep submucosa invasion and/or high-risk lesions (i.e., lymphovascular invasion, poorly differentiated histology, positive margins).[88]

Patients who are unsuitable for or decline surgery can be offered definitive chemoradiotherapy. The radiation component should be delivered at a dose of 50.4 Gy. The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; fluorouracil plus oxaliplatin; or folinic acid plus fluorouracil plus oxaliplatin (FOLFOX). Other options include: cisplatin plus fluorouracil; cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil.[15] [88][150] [152][171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Definitive chemoradiotherapy has been shown to increase the survival of patients who have squamous cell carcinoma or adenocarcinoma of the oesophagus, T1-3 N0-1 M0, compared with radiotherapy alone.[173] [174] The landmark RTOG 85-01 trial randomised patients to receive either chemoradiotherapy (fluorouracil plus cisplatin plus radiotherapy) or radiotherapy alone. At 5 years of

follow-up, the overall survival for combined therapy was 26% (95% CI 15% to 37%) compared with 0% following radiotherapy.[174] Median survival in one phase 3 study (n=121) was 12.5 months in patients treated with chemoradiotherapy compared with 8.9 months in the patients treated with radiotherapy alone.[173]

Endoscopic therapy is an alternative to chemoradiotherapy, but only for patients with superficial adenocarcinomas.[88]

Localised disease (cT2, cN0, M0)

Oesophagectomy is recommended as part of the treatment plan for patients with localised disease (cT2, cN0, M0) who are suitable for surgery.[15] [88][131]

Certain patients may be considered for surgery with either preoperative chemoradiotherapy or perioperative (i.e., pre- and postoperative) chemotherapy, depending on histology subtype and histopathological findings.

Preoperative treatment is used to reduce the size of the primary tumour and remove micrometastatic disease, with the aim of improving R0 (no residual disease) resection rates, reducing the risk of recurrence and metastases, and improving survival rates.[175]

Localised disease and low-risk lesions

Patients with cT2 disease and low-risk lesions (i.e., no lymphovascular invasion, tumour size <30 mm, well-differentiated histology) can be treated with surgery alone if there is confidence in the accuracy of the clinical stage.[15] [131] [176] [177] European guidelines note that there is insufficient evidence to make firm recommendations regarding the use of preoperative chemoradiotherapy or chemotherapy for T2 N0 cancers, advising that each case should be discussed by a multidisciplinary team with careful consideration of the risks and benefits.[88]

Localised disease and high-risk lesions: squamous cell carcinoma

Patients with localised oesophageal squamous cell carcinoma (OSCC) and high-risk lesions (i.e., lymphovascular invasion, tumour size ≥30 mm, poorly differentiated histology) can be considered for preoperative chemoradiation therapy followed by surgery.[15] [88] [131][178] This has been shown to improve survival compared with surgery alone in patients with localised or locally advanced OSCC.[150] [178] [179][180] [181]

The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy), based on the results from the CROSS trial (which enrolled patients with cT1, N1 disease or cT2-3, N0-1 disease).[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Localised disease and high-risk lesions: adenocarcinoma

Patients with localised oesophageal adenocarcinoma (OAC) and high-risk lesions can be considered for surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy in 23 fractions), based on the results from the CROSS trial.[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Patients with resectable disease should proceed to surgery even after complete clinical tumour response to preoperative chemoradiation therapy, as data for a watch-and-wait strategy are limited.[88]

Perioperative chemotherapy is an alternative treatment, with data strongly suggesting non-inferiority compared to preoperative chemoradiation.[15] The survival benefit of perioperative chemotherapy was first demonstrated in the phase 3 MAGIC trial, which compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil (ECF) to surgery alone. It found that perioperative chemotherapy improves progression-free and overall survival in patients with non-metastatic stage 2 and higher gastric or oesophago-gastric junction adenocarcinoma.[184] The phase 3 Neo-AEGIS trial directly compared preoperative chemoradiation (CROSS regimen) to perioperative chemotherapy (modified MAGIC or FLOT regimen) in patients with locoregional adenocarcinoma of the oesophagus or oesophago-gastric junction.[185] Both treatment arms showed similar 3-year survival and no major differences in operative and health-related quality of life outcomes. The trial was prematurely terminated due to similar survival metrics and the impact of the COVID-19 pandemic.[185]

The role of perioperative chemotherapy versus upfront chemoradiation is under active investigation. The phase 3 ESOPEC trial, which compared the efficacy of neoadjuvant chemoradiation (CROSS protocol) followed by surgery with perioperative chemotherapy (FLOT protocol) and surgery in patients with resectable, locally advanced adenocarcinoma, found a 29-month improvement in median overall survival with perioperative chemotherapy regimen compared with neoadjuvant chemoradiation regimen.[186] [187] Similar surgical complications and postoperative mortality were reported in both arms. These results suggest the superiority of perioperative FLOT protocol over neoadjuvant CROSS protocol in patients with resectable, locally advanced adenocarcinoma.[187]

The preferred perioperative chemotherapy regimens are fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT), or a fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin. The other option is fluorouracil plus cisplatin.[15] [88]

Localised disease: unsuitable for surgery

Patients with localised squamous cell carcinoma or adenocarcinoma who are unsuitable for surgery (e.g., those with tumours located in the cervical oesophagus, where surgery would entail a laryngectomy) or who decline surgery can be considered for definitive chemoradiotherapy.[15] [88]

Randomised trials comparing definitive chemoradiotherapy versus surgery plus preoperative chemoradiotherapy in patients with locally advanced disease have reported similar survival outcomes, particularly among those with squamous cell carcinoma who achieved a complete response with chemoradiotherapy.[188] [189] [190]

Close monitoring is required following definitive chemoradiotherapy due to the risk of local tumour recurrence.[188] [189]

Salvage oesophagectomy can be considered in patients with persistent or progressive disease post definitive chemoradiotherapy. It has been shown to be comparable in terms of outcomes to those with planned trimodality therapy in the setting of adenocarcinoma.[88] [191] [192] However, some data suggest increased morbidity for patients with ESCC.[193]

Radiotherapy should be delivered at a dose of 50.4 Gy. The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; fluorouracil plus oxaliplatin; or folinic acid plus fluorouracil plus oxaliplatin (FOLFOX). Other options include: cisplatin plus fluorouracil; cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil.[15] [88] [150] [152] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Locally advanced disease (cT3-T4 or cN1-3, M0)

Multimodality treatment comprising surgery combined with preoperative chemoradiotherapy, preoperative chemotherapy, or perioperative (i.e., pre- and postoperative) chemotherapy is recommended for patients with locally advanced disease (cT3-T4 or cN1-3, M0) who are suitable for surgery.[15] [88] [131] [178]

Decisions regarding the use of preoperative or perioperative treatment can be guided by histology subtype (squamous cell carcinoma or adenocarcinoma).

Similar to patients with localised (cT2) disease, the goal of preoperative and perioperative treatment in patients with locally advanced disease is to improve R0 resection rates, reduce the risk of recurrence and metastases, and improve survival.[175] Preoperative treatment is particularly important for locally advanced disease because approximately 30% to 40% of patients have resectable disease at presentation.[194]

Furthermore, survival rates are relatively low for those treated with surgery alone.[195] [196]

Locally advanced disease: squamous cell carcinoma

The recommended initial treatment for patients with locally advanced OSCC is surgery plus preoperative chemoradiotherapy.[15] [88] [131] [147][178] This has been shown to improve survival compared with surgery alone in patients with localised or locally advanced OSCC.[131] [150] [179] [180] [181]

The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy), based on the results from the CROSS trial (which enrolled patients with cT1, N1 disease or cT2-3, N0-1 disease).[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Locally advanced disease: adenocarcinoma

The recommended initial treatment for patients with locally advanced OAC is surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[15] [88] [131] [147] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy in 23 fractions), based on the results from the CROSS trial.[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include:

fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

Perioperative chemotherapy is an alternative treatment for locally advanced OAC, with data strongly suggesting non-inferiority compared to preoperative chemoradiation.[15] The role of perioperative chemotherapy versus upfront chemoradiation is under active investigation. The phase 3 ESOPEC trial, which compared the efficacy of neoadjuvant chemoradiation (CROSS protocol) followed by surgery with perioperative chemotherapy (FLOT protocol) and surgery in patients with resectable, locally advanced adenocarcinoma, found a 29-month improvement in median overall survival with perioperative chemotherapy regimen compared with neoadjuvant chemoradiation regimen.[186] [187] Similar surgical complications and postoperative mortality were reported in both arms. These results suggest the superiority of perioperative FLOT protocol over neoadjuvant CROSS protocol in patients with resectable, locally advanced adenocarcinoma.[187]

The preferred perioperative chemotherapy regimens are fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT), a fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin. The other option is fluorouracil plus cisplatin.[15] [88]

Patients with resectable disease should proceed to surgery even after complete clinical tumour response to preoperative chemoradiotherapy, as data for a watch-and-wait strategy are limited.[88]

Locally advanced disease: unsuitable for surgery

Patients with locally advanced squamous cell carcinoma or adenocarcinoma who are unsuitable for surgery (e.g., those with tumours located in the cervical oesophagus, where surgery would entail a laryngectomy) or who decline surgery can be considered for definitive chemoradiotherapy.[15] [88] [131]

Randomised trials comparing definitive chemoradiotherapy versus surgery plus preoperative chemoradiotherapy in patients with locally advanced disease have reported similar survival outcomes, particularly among those with squamous cell carcinoma who achieved a complete response with chemoradiotherapy.[188] [189] [190]

Close monitoring is required following definitive chemoradiotherapy due to the risk of local tumour recurrence.[188] [189] In the case of complete response to definitive chemoradiotherapy, a 3-month follow-up with endoscopy, biopsies, and computed tomography (CT) scan should be considered.[88]

Salvage oesophagectomy can be considered in patients with persistent or progressive disease post chemoradiotherapy. It has been shown to be comparable in terms of outcomes to those with planned trimodality therapy in the setting of adenocarcinoma.[88] [191] [192] However, some data suggest increased morbidity for patients with ESCC.[193]

The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; oxaliplatin plus fluorouracil; or fluorouracil plus folinic acid plus oxaliplatin (FOLFOX). Other options include: cisplatin plus fluorouracil; cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil. [15] [88] [150] [152] [171] [172] In one randomised trial, chemoradiotherapy with FOLFOX did not increase progression-free survival compared with chemoradiotherapy with fluorouracil plus cisplatin; however, FOLFOX might be a more convenient option for patients with localised oesophageal cancer unsuitable for surgery.[152] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

The radiation component of the treatment should be delivered using 3D conformal radiation treatment (RT) as a minimum, but intensity-modulated RT or volumetric arc therapy are preferred to better minimise the radiation dose to normal tissues such as the heart and lungs. There is little evidence to support the use of RT doses >50.4 Gy in the definitive treatment of oesophageal cancer.[88]

Targeted therapy may be added to chemotherapy regimens for certain subtypes of unresectable, locally advanced oesophageal cancer. It is important that all patients with oesophageal cancer undergo biomarker testing (e.g., for HER2, MSI-H, dMMR, and PD-L1 overexpression) to identify those suitable for targeted therapies.The preferred options include trastuzumab, nivolumab, and pembrolizumab. The preferred treatment options for MSI-H/dMMR tumours include pembrolizumab (alone or in combination with fluoropyrimidine- and platinum-based chemotherapy), dostarlimab, and nivolumab (in combination with ipilimumab or fluoropyrimidine- and platinum-based chemotherapy).

Second-line or subsequent therapy depends on prior therapy and performance status.[15] If patients are unable to tolerate chemoradiotherapy they should be offered palliative radiotherapy or best supportive care.[15]

Postoperative residual pathological disease

Patients with localised or locally advanced disease (both squamous cell carcinoma and adenocarcinoma) who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199] Other recommended regimens are capecitabine and oxaliplatin or fluorouracil and oxaliplatin.[15]

In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] PD-L1 testing is not required for this indication.[88]

Metastatic (M1) disease

Patients presenting with distant metastatic disease are considered to have unresectable disease. Early palliative therapy and best supportive care are recommended for these patients.[15] [88][199] [200]

Patients may have symptoms secondary to the local and systemic effects of malignancy, such as dysphagia, oesophageal obstruction, pain, bleeding, and malaise, in addition to underlying comorbidities. Palliation of symptoms and maintaining quality of life is, therefore, central to managing patients with metastatic disease.

Dysphagia and oesophageal obstruction may be relieved using palliative radiotherapy (external beam radiotherapy or brachytherapy) or self-expanding metallic stent insertion, depending on the degree of dysphagia and its impact on nutrition, quality of life, performance status, and prognosis.[15] [88] [133] The National Institute for Health and Care Excellence in the UK advises against routine use of external beam radiotherapy after stent placement in patients with oesophageal cancer and recommends that it should only be used in those with oesophageal cancer having prolonged post-interventional bleeding or a known bleeding disorder.[133] If there is complete obstruction, endoscopic lumen restoration should be performed via simultaneous retrograde and anterograde enteroscopy.[15] Severe obstruction should be relieved with wire-guided dilation or balloon dilation and insertion of an expandable metal stent.[15] These

options should be considered for moderate obstruction, balancing the associated risks and benefits.[15] Photodynamic therapy may be effective but is less commonly used due to associated photosensitivity and costs.[15] Surgery may be useful in carefully selected patients.[15]

Nutritional status should be optimised with dietetic input (including dietary advice, nutritional supplements, and, if appropriate, short-term enteral feeding).

Patients with metastatic disease can be considered for chemotherapy, in addition to best supportive care. The decision to proceed with chemotherapy should be based on performance status, comorbidities, and patient preference.

Chemotherapy may improve symptoms, survival, and quality of life compared with best supportive care alone in patients with metastatic disease.[201] [202] Most of the evidence supporting the use of chemotherapy in metastatic disease is extrapolated from randomised studies in patients with advanced/metastatic gastric adenocarcinoma.[201] [202]

Two-drug chemotherapy regimens comprising a platinum agent (e.g., oxaliplatin or cisplatin) plus a fluoropyrimidine (e.g., fluorouracil or capecitabine) are typically recommended for first-line treatment in patients with metastatic disease.[15] [88] Studies suggest equivalence for oxaliplatin and cisplatin.[88] Oxaliplatin is usually preferred to cisplatin due to lower toxicity.[15] [203] A reduced-dose oxaliplatin plus capecitabine regime is an option for older or frail patients who may be unsuitable for full-dose treatment.[88]

Adding a taxane (docetaxel) or anthracycline (epirubicin) to a two-drug regimen (i.e., triplet therapy) may be considered if a rapid response is required (e.g., to treat bulky and/or symptomatic disease). However, triplet therapy is associated with an increased risk of toxicity and adverse effects (e.g., myelosuppression, gastrointestinal toxicity, neuropathy, neutropenia); therefore, it is only suitable for fit patients with good performance status.[204] [205] [206]

Docetaxel combined with cisplatin plus fluorouracil has been shown to improve survival compared with cisplatin plus fluorouracil alone in patients with untreated advanced gastric cancer, although at the expense of increased toxicity.[205]

Epirubicin combined with cisplatin plus fluorouracil has been shown to improve survival compared with other triplet regimens (e.g., fluorouracil plus doxorubicin plus methotrexate; and mitomycin plus cisplatin plus fluorouracil) in patients with advanced oesophago-gastric cancer.[207] [208] However, there is controversy regarding the efficacy and safety of epirubicin-containing regimens, particularly when compared with standard two-drug regimens.[209]

Other triplet therapy regimens that can be considered for first-line treatment include folinic acid plus fluorouracil plus oxaliplatin (FOLFOX), and folinic acid plus fluorouracil plus irinotecan (FOLFIRI).[210] [211] [212]

Despite the benefits of triplet therapy, two-drug regimens are generally preferred due to lower toxicity.

Other options for first-line therapy include docetaxel plus cisplatin; paclitaxel plus cisplatin; paclitaxel plus carboplatin; or single-agent capecitabine, fluorouracil, docetaxel, or paclitaxel.[15]

Several targeted therapies can be used in patients with metastatic oesophageal and oesophageal junction cancer.

It is important that all patients with oesophageal cancer undergo biomarker testing (e.g., for HER2, MSI-H, dMMR, and PD-L1 overexpression) to identify those suitable for targeted therapies. The preferred options include trastuzumab, pembrolizumab, and nivolumab. Trastuzumab is added to chemotherapy for HER2 overexpression positive tumours. The preferred treatment options for MSI-H/dMMR tumours include pembrolizumab (alone or in combination with fluoropyrimidine- and platinum-based chemotherapy), dostarlimab, and nivolumab (in combination with ipilimumab or fluoropyrimidine- and platinum-based chemotherapy). Second-line or subsequent therapy depends on prior therapy and performance status.[15]

Recurrent disease

Treatment decisions for patients with recurrent or refractory disease are informed by prior treatment history.

Patients with locoregional recurrence that occurs subsequent to chemoradiotherapy can be considered for surgery if the tumour is resectable (depending on performance status and patient preference).

Patients with locoregional recurrence that occurs following surgery without the use of chemoradiotherapy can be considered for chemoradiotherapy, surgery, chemotherapy, and palliative care/best supportive care (depending on performance status and patient preference).

Patients with unresectable recurrent disease or metastatic disease that occurs following treatment can be considered for palliative/best supportive care (including systemic and targeted therapies).

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
limited disease (cT1, cN0, M0)		
T1a disease	1st	endoscopic therapy or surgery (oesophagectomy)
T1b disease: suitable for surgery	1st	surgery (oesophagectomy) or endoscopic therapy
T1b disease: not suitable for surgery	1st	definitive chemoradiotherapy
	2nd	endoscopic therapy
localised disease (cT2, cN0, M0): suitable for surgery		
low-risk lesions	1st	surgery (oesophagectomy)
high-risk lesions: squamous cell carcinoma	1st	surgery (oesophagectomy)
	plus	preoperative chemoradiotherapy
	adjunct	postoperative nivolumab
high-risk lesions: adenocarcinoma	1st	surgery (oesophagectomy)
	plus	preoperative chemoradiotherapy
	adjunct	postoperative nivolumab
	1st	surgery (oesophagectomy)
	plus	perioperative chemotherapy
	adjunct	postoperative nivolumab
localised disease (cT2, cN0, M0): unsuitable for surgery		
	1st	definitive chemoradiotherapy
locally advanced disease (cT3-4, cN1-3, M0): suitable for surgery		
squamous cell carcinoma	1st	surgery (oesophagectomy)
	plus	preoperative chemoradiotherapy
	adjunct	postoperative nivolumab

Acute (summary)		
adenocarcinoma	1st	surgery (oesophagectomy)
	plus	preoperative chemoradiotherapy
	adjunct	postoperative nivolumab
	1st	surgery (oesophagectomy)
	plus	perioperative chemotherapy
	adjunct	postoperative nivolumab
locally advanced disease (cT3-4, cN1-3, M0): unsuitable for surgery		
	1st	definitive chemoradiotherapy
	adjunct	targeted therapy
metastatic (M1) disease		
	1st	palliative chemotherapy
	plus	best supportive care
	adjunct	targeted therapy

Ongoing (summary)		
recurrent disease		
locoregional recurrence	1st	surgery or chemoradiotherapy or chemotherapy and/or palliative/best supportive care
unresectable or metastatic recurrence	1st	palliative/best supportive care

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

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limited disease (cT1, cN0, M0)

T1a disease — **1st** — **endoscopic therapy or surgery (oesophagectomy)**

» Endoscopic therapy alone is recommended for most patients with cT1a disease (i.e., disease limited to the lamina propria and muscularis mucosae).[15] [88] No further surgical treatment is required. Endoscopic resection can usually be considered curative in all T1a adenocarcinomas.[88] Oesophageal squamous cell carcinomas have a higher risk of lymph node metastasis, and features such as differentiation and lymphovascular invasion should be considered. Oesophagectomy is therefore indicated for patients with extensive T1a disease, particularly nodular disease that is not controlled with endoscopic therapy.[15] [88]

» In a SEER database analysis of 1458 patients with T1N0 oesophageal cancer, the overall survival rates were similar after treatment with surgery or endoscopic therapy, but those treated with endoscopic therapy had improved cancer-specific survival and decreased morbidity.[168]

» Residual Barrett's oesophagus should be ablated following endoscopic therapy to minimise the risk of subsequent cancer.[15][88] Following endoscopic therapy, patients require continuous monitoring with routine interval endoscopies.

T1b disease: suitable for surgery — **1st** — **surgery (oesophagectomy) or endoscopic therapy**

» Oesophagectomy is recommended for patients with cT1b disease (squamous cell carcinoma or adenocarcinoma) who are suitable for surgery.[15] [88] [133][169] [170] Patients with superficial T1b adenocarcinomas may be considered for initial treatment with endoscopic therapy instead of surgery.[88] If histopathological assessment of endoscopic resected specimens confirms superficial T1b disease (i.e., submucosa invasion <500 micrometres for adenocarcinoma), no ulceration, and the presence of low-risk lesions (i.e., no lymphovascular invasion; well differentiated histology; negative margins) then no further surgical treatment is required. The American

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Society for Gastrointestinal Endoscopy suggests that patients with oesophageal squamous cell dysplasia or early, well-differentiated, non-ulcerated oesophageal squamous cell carcinoma who do not show overt signs of submucosal invasion need not undergo surgical resection.[138] Surgery is required if histopathological assessment confirms deep submucosa invasion and/or high-risk lesions (i.e., lymphovascular invasion; poorly differentiated histology; positive margins).[88]

T1b disease: not suitable for surgery — **1st** — **definitive chemoradiotherapy**

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

OR

» folinic acid
-and-
» fluorouracil
-and-
» oxaliplatin

Secondary options

» cisplatin
-and-
» fluorouracil

OR

» cisplatin
-and-
» docetaxel

OR

» cisplatin
-and-
» paclitaxel

OR

» irinotecan
-and-
» cisplatin

Acute

OR

» paclitaxel
-and-
» fluorouracil

» Patients who are unsuitable for or decline surgery can be offered definitive chemoradiotherapy. The radiation component should be delivered at a dose of 50.4 Gy. The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; fluorouracil plus oxaliplatin; or folinic acid plus fluorouracil plus oxaliplatin (FOLFOX). Other options include: cisplatin plus fluorouracil; cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil.[15] [88][150] [152] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

» Definitive chemoradiotherapy has been shown to increase the survival of patients who have squamous cell carcinoma or adenocarcinoma of the oesophagus, T1-3 N0-1 M0, compared with radiotherapy alone.[173] [174] The landmark RTOG 85-01 trial randomised patients to receive either chemoradiotherapy (fluorouracil plus cisplatin plus radiotherapy) or radiotherapy alone. At 5 years of follow-up, the overall survival for combined therapy was 26% (95% CI 15% to 37%) compared with 0% following radiotherapy.[174] Median survival in one phase 3 study (n=121) was 12.5 months in patients treated with chemoradiotherapy compared with 8.9 months in the patients treated with radiotherapy alone.[173]

» See local specialist protocol for dosing guidelines.

2nd **endoscopic therapy**

» Endoscopic therapy is an alternative to chemoradiotherapy but only for patients with superficial adenocarcinomas.[88]

localised disease (cT2, cN0, M0): suitable for surgery

low-risk lesions

1st **surgery (oesophagectomy)**

» Surgery (oesophagectomy) is the recommended initial treatment for patients with localised disease (cT2, cN0, M0) who are suitable for surgery.[15] [88] [131]

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» Patients with cT2 disease and low-risk lesions (i.e., no lymphovascular invasion; tumour size <30 mm; well-differentiated histology) can be treated with surgery alone if there is confidence in the accuracy of the clinical stage.[15] [131] [176] [177]

high-risk lesions: squamous cell carcinoma

1st **surgery (oesophagectomy)**

» Surgery (oesophagectomy) is the recommended initial treatment for patients with localised disease (cT2, cN0, M0) who are suitable for surgery.[15] [88] [131]

plus **preoperative chemoradiotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» Patients with localised squamous cell carcinoma and high-risk lesions (i.e., lymphovascular invasion; tumour size ≥30 mm; poorly differentiated histology) can be considered for preoperative chemoradiotherapy followed by surgery.[15] [88] [131][178] This has been shown to improve survival compared with surgery alone in patients with localised or

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locally advanced oesophageal squamous cell carcinoma.[150][178] [179] [180] [181]

» The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy), based on the results from the CROSS trial (which enrolled patients with cT1, N1 disease or cT2-3, N0-1 disease).[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

high-risk lesions: adenocarcinoma **1st** **surgery (oesophagectomy)**

» Surgery (oesophagectomy) is the recommended initial treatment for patients with localised disease (cT2, cN0, M0) who are suitable for surgery.[15] [88] [131]

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plus **preoperative chemoradiotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» Patients with localised oesophageal adenocarcinoma (OAC) and high-risk lesions can be considered for surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[15] [88][131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

» The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy in 23 fractions), based on the results from the CROSS trial.[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15]Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is

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an alternative to fluorouracil for patients who are capable of swallowing tablets.

» Patients with resectable disease should proceed to surgery even after complete clinical tumour response to preoperative chemoradiotherapy, as data for a watch-and-wait strategy are limited.[88]

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

1st **surgery (oesophagectomy)**

» Surgery (oesophagectomy) is the recommended initial treatment for patients with localised disease (cT2, cN0, M0) who are suitable for surgery.[15] [88] [131]

plus **perioperative chemotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluorouracil
-and-

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» folinic acid
-and-
» oxaliplatin
-and-
» docetaxel

OR

» fluorouracil
-or-
» capecitabine
--AND--
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

» Patients with localised oesophageal adenocarcinoma (OAC) and high-risk lesions can be considered for surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[15] [88] [131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

» The preferred perioperative chemotherapy regimens for T2 tumours are fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT), or a fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin. The other option is fluorouracil plus cisplatin.[15] [88]

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint

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inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

localised disease (cT2, cN0, M0): unsuitable for surgery

1st **definitive chemoradiotherapy**

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

OR

» folinic acid
-and-
» fluorouracil
-and-
» oxaliplatin

Secondary options

» cisplatin
-and-
» fluorouracil

OR

» cisplatin
-and-
» docetaxel

OR

» cisplatin
-and-

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Acute

» paclitaxel

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» Patients with localised squamous cell carcinoma or adenocarcinoma who are unsuitable for surgery (e.g., those with tumours located in the cervical oesophagus) or who decline surgery can be considered for definitive chemoradiotherapy.[15][88]

» Randomised trials comparing definitive chemoradiotherapy versus surgery plus preoperative chemoradiotherapy in patients with locally advanced disease have reported similar survival outcomes, particularly among those with squamous cell carcinoma who achieved a complete response with chemoradiotherapy.[188] [189] [190]

» Close monitoring is required following definitive chemoradiotherapy due to the risk of local tumour recurrence.[188] [189]

» Salvage oesophagectomy can be considered in patients with persistent or progressive disease post definitive chemoradiotherapy. It has been shown to be comparable in terms of outcomes to those with planned trimodality therapy in the setting of adenocarcinoma.[88] [191] [192] However, some data suggest increased morbidity for patients with oesophageal squamous cell carcinoma.[193]

» Radiotherapy should be delivered at a dose of 50.4 Gy. The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; fluorouracil plus oxaliplatin; or fluorouracil plus folinic acid plus oxaliplatin (FOLFOX). Other options are: cisplatin plus fluorouracil; cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil.[15] [88] [150] [152] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

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» See local specialist protocol for dosing guidelines.

locally advanced disease (cT3-4, cN1-3, M0): suitable for surgery

squamous cell carcinoma

1st **surgery (oesophagectomy)**

» The recommended initial treatment for patients with locally advanced oesophageal squamous cell carcinoma (OSCC) is surgery plus preoperative chemoradiotherapy.[15] [88] [131][178] This has been shown to improve survival compared with surgery alone in patients with localised or locally advanced OSCC.[131] [150] [179] [180] [181]

plus **preoperative chemoradiotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» The recommended initial treatment for patients with locally advanced oesophageal squamous cell carcinoma (OSCC) is surgery plus preoperative chemoradiotherapy.[15] [88] [131][178] This has been shown to improve survival compared with surgery alone in patients

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with localised or locally advanced OSCC.[131] [150] [179] [180] [181]

» The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy), based on the results from the CROSS trial (which enrolled patients with cT1, N1 disease or cT2-3, N0-1 disease).[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include: fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

adenocarcinoma **1st** **surgery (oesophagectomy)**

» The recommended initial treatment for patients with locally advanced oesophageal adenocarcinoma (OAC) is surgery plus preoperative chemoradiotherapy or perioperative

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chemotherapy.[15] [88][131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

plus **preoperative chemoradiotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» The recommended initial treatment for patients with locally advanced oesophageal adenocarcinoma (OAC) is surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[15] [88] [131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

» The standard regimen for preoperative chemoradiotherapy is carboplatin plus paclitaxel plus radiotherapy (41.4 Gy in 23 fractions), based on the results from the CROSS trial.[150] [180] [181] The other preferred regimen is fluorouracil plus oxaliplatin plus radiotherapy.[15] Other recommended regimens include:

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fluorouracil plus cisplatin plus radiotherapy; irinotecan plus cisplatin plus radiotherapy; and paclitaxel plus fluorouracil plus radiotherapy.[15] [88] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

» Patients with resectable disease should proceed to surgery even after complete clinical tumour response to preoperative chemoradiotherapy, as data for a watch-and-wait strategy are limited.[88]

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

1st **surgery (oesophagectomy)**

» The recommended initial treatment for patients with locally advanced oesophageal adenocarcinoma (OAC) is surgery plus preoperative chemoradiotherapy or perioperative chemotherapy.[15] [88][131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

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plus **perioperative chemotherapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» fluorouracil
-and-
» folinic acid
-and-
» oxaliplatin
-and-
» docetaxel

OR

» fluorouracil
-or-
» capecitabine
--AND--
» oxaliplatin

Secondary options

» fluorouracil
-and-
» cisplatin

» Perioperative chemotherapy is an alternative to preoperative chemoradiotherapy for locally advanced oesophageal adenocarcinoma (OAC), with data strongly suggesting non-inferiority.[15] [88] [131] Both approaches have been found to improve survival and R0 resection rates compared with surgery alone in patients with localised or locally advanced OAC.[150] [179] [180] [181] [182] [183]

» The preferred perioperative chemotherapy regimens are fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT), or a fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin. The other option is fluorouracil plus cisplatin.[15] [88]

» See local specialist protocol for dosing guidelines.

adjunct **postoperative nivolumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» nivolumab

» Patients with localised disease who have residual pathological disease despite

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complete surgical resection and preoperative chemoradiotherapy (i.e., ≥ypT1 or ypN1) are at high risk for recurrence, particularly if there is lymph node involvement.[197] These patients can be considered for postoperative treatment with nivolumab, an immune checkpoint inhibitor that blocks the programmed cell death-1 receptor (PD-1).[15] [198] [199]

» In the CheckMate 577 study, nivolumab significantly improved disease-free survival compared with placebo in patients with localised or locally advanced disease who had residual pathological disease following complete surgical resection and preoperative chemoradiotherapy (22.4 vs. 11.0 months).[198] Programmed death-ligand 1 (PD-L1) testing is not required for this indication.[88]

» See local specialist protocol for dosing guidelines.

locally advanced disease (cT3-4, cN1-3, M0): unsuitable for surgery

1st **definitive chemoradiotherapy**

Primary options

» carboplatin
-and-
» paclitaxel

OR

» fluorouracil
-and-
» oxaliplatin

OR

» folinic acid
-and-
» fluorouracil
-and-
» oxaliplatin

Secondary options

» cisplatin
-and-
» fluorouracil

OR

» cisplatin
-and-
» docetaxel

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OR

» cisplatin
-and-
» paclitaxel

OR

» irinotecan
-and-
» cisplatin

OR

» paclitaxel
-and-
» fluorouracil

» Patients with locally advanced squamous cell carcinoma or adenocarcinoma who are unsuitable for surgery (e.g., those with tumours located in the cervical oesophagus) or who decline surgery can be considered for definitive chemoradiotherapy.[131]

» Randomised trials comparing definitive chemoradiotherapy versus surgery plus preoperative chemoradiotherapy in patients with locally advanced disease have reported similar survival outcomes, particularly among those with squamous cell carcinoma who achieved a complete response with chemoradiotherapy.[188] [189] [190]

» Close monitoring is required following definitive chemoradiotherapy due to the risk of local tumour recurrence.[188] [189] In the case of complete response to definitive chemoradiotherapy, a 3-month follow-up with endoscopy, biopsies, and computed tomography (CT) scan should be considered.[88]

» Salvage oesophagectomy can be considered in patients with persistent or progressive disease post chemoradiotherapy. It has been shown to be comparable in terms of outcomes to those with planned trimodality therapy in the setting of adenocarcinoma.[88] [191] [192] However, some data suggest increased morbidity for patients with oesophageal squamous cell carcinoma.[193]

» The first-line regimens for the chemotherapy backbone are: carboplatin plus paclitaxel; fluorouracil plus oxaliplatin; or fluorouracil plus folinic acid plus oxaliplatin (FOLFOX). Other options include: cisplatin plus fluorouracil;

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cisplatin plus docetaxel or paclitaxel; irinotecan plus cisplatin; or paclitaxel plus fluorouracil.[15] [88][150] [152] [171] [172] Capecitabine is an alternative to fluorouracil for patients who are capable of swallowing tablets.

» The radiation component of the treatment should be delivered using 3D conformal radiation treatment (RT) as a minimum, but intensity-modulated RT or volumetric arc therapy are preferred to better minimise the radiation dose to normal tissues such as the heart and lungs. There is little evidence to support the use of RT doses >50.4 Gy in the definitive treatment of oesophageal cancer.[88]

» If patients are unable to tolerate chemoradiotherapy they should be offered palliative radiotherapy or best supportive care.[15]

» See local specialist protocol for dosing guidelines.

adjunct **targeted therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» trastuzumab

OR

» pembrolizumab

OR

» nivolumab

OR

» nivolumab
-and-
» ipilimumab

OR

» dostarlimab

» It is important that all patients with oesophageal cancer undergo biomarker testing (e.g., for human epidermal receptor 2 [HER2], metastatic microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], and programmed death-ligand 1 [PD-L1] overexpression) to identify those suitable for

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targeted therapies.These agents may be used alone or in combination with chemotherapy.

» Available preferred options include trastuzumab, nivolumab, and pembrolizumab. The preferred options for MSI-H/dMMR tumours include pembrolizumab (alone or in combination with fluoropyrimidine- and platinum-based chemotherapy), dostarlimab, and nivolumab (in combination with ipilimumab or fluoropyrimidine- and platinum-based chemotherapy).[15]

» Trastuzumab (an anti-HER2 monoclonal antibody) is approved for use in patients with previously untreated metastatic HER2-positive adenocarcinoma, in combination with first-line platinum- and fluoropyrimidine-based chemotherapy.[15] [114] [154] In the ToGA trial, trastuzumab combined with chemotherapy (cisplatin plus either capecitabine or fluorouracil) improved survival (16.0 vs. 11.8 months) in patients with HER2-positive oesophageal and gastric adenocarcinoma compared with chemotherapy alone.[114]

» Pembrolizumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line therapy with a fluoropyrimidine, a platinum agent, and trastuzumab for patients with HER2-positive adenocarcinoma.[15] [155] Pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy may be used for the first-line treatment of patients with squamous cell carcinoma or HER2-negative adenocarcinoma. [15] [88][155] In Europe, this approval is limited to patients with combined positive score (CPS) ≥10. In the KEYNOTE-859 study comprising patients with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma, the combination of pembrolizumab with chemotherapy has shown significant and clinically meaningful improvement in overall survival with manageable toxicity, compared with placebo.[156]

» Nivolumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line treatment with fluoropyrimidine- and platinum-based chemotherapy for patients HER2-negative with advanced oesophageal or oesophago-gastric junction adenocarcinoma.[15] [155] The National Institute for Health and Care Excellence (NICE) in the UK recommends nivolumab after fluoropyrimidine and platinum-based therapy for the treatment of previously treated unresectable advanced, recurrent, or metastatic oesophageal

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squamous cell carcinoma in adults.[157] NICE further recommends nivolumab plus fluoropyrimidine-based and platinum-based therapy as an option in adults with untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 at a level of 1% or more when pembrolizumab plus chemotherapy is not found to be suitable.[158] Nivolumab is approved in combination with fluoropyrimidine- and platinum-based chemotherapy and in combination with ipilimumab for the first-line treatment of patients with advanced oesophageal squamous cell carcinoma.[15] [155]

» Dostarlimab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) is approved for the treatment of patients with DNA mismatch repair-deficiency recurrent or advanced solid tumours that have progressed on or following prior treatment, who have no alternative treatment options, and who have not previously received a PD-1 or PD-L1 inhibitor.[15]

» Second-line or subsequent therapy depends on prior therapy and performance status.[15]

» See local specialist protocol for dosing guidelines.

metastatic (M1) disease

1st **palliative chemotherapy**

Primary options

» oxaliplatin
-and-
» fluorouracil

OR

» oxaliplatin
-and-
» capecitabine

OR

» cisplatin
-and-
» fluorouracil

OR

» cisplatin
-and-

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» capecitabine

OR

» docetaxel
-and-
» cisplatin
-and-
» fluorouracil

OR

» docetaxel
-and-
» cisplatin

OR

» paclitaxel
-and-
» cisplatin

OR

» paclitaxel
-and-
» carboplatin

OR

» fluorouracil
-and-
» folinic acid
-and-
» oxaliplatin

OR

» fluorouracil
-and-
» folinic acid
-and-
» irinotecan

OR

» capecitabine

OR

» fluorouracil

OR

Acute

» docetaxel

OR

» paclitaxel

» Patients with metastatic disease can be considered for chemotherapy, in addition to best supportive care. The decision to proceed with chemotherapy should be based on performance status, comorbidities, and patient preference.

» Chemotherapy may improve symptoms, survival, and quality of life compared with best supportive care alone in patients with metastatic disease.[201] [202] Most of the evidence supporting the use of chemotherapy in metastatic disease is extrapolated from randomised studies in patients with advanced/metastatic gastric adenocarcinoma.[201] [202]

» Two-drug chemotherapy regimens comprising a platinum agent (e.g., oxaliplatin or cisplatin) plus a fluoropyrimidine (e.g., fluorouracil or capecitabine) are typically recommended for first-line treatment in patients with metastatic disease.[15] [88] Studies suggest equivalence for oxaliplatin and cisplatin.[88] Oxaliplatin is usually preferred to cisplatin due to lower toxicity.[15] [203] A reduced-dose oxaliplatin plus capecitabine regime is an option for older or frail patients who may be unsuitable for full-dose treatment.[88]

» Adding a taxane (docetaxel) or anthracycline (epirubicin) to a two-drug regimen (i.e., triplet therapy) may be considered if a rapid response is required (e.g., to treat bulky and/or symptomatic disease). However, triplet therapy is associated with an increased risk of toxicity and adverse effects (e.g., myelosuppression, gastrointestinal toxicity, neuropathy, neutropenia); therefore, it is only suitable for fit patients with good performance status.[204] [205] [206]

» Docetaxel combined with cisplatin plus fluorouracil has been shown to improve survival compared with cisplatin plus fluorouracil alone in patients with untreated advanced gastric cancer, although at the expense of increased toxicity.[205]

» Epirubicin combined with cisplatin plus fluorouracil has been shown to improve survival compared with other triplet regimens (e.g., fluorouracil plus doxorubicin plus methotrexate; and mitomycin plus cisplatin

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plus fluorouracil) in patients with advanced oesophago-gastric cancer.[207] [208] However, there is controversy regarding the efficacy and safety of epirubicin-containing regimens, particularly when compared with standard two-drug regimens.[209]

» Other triplet therapy regimens that can be considered for first-line treatment include folinic acid plus fluorouracil plus oxaliplatin (FOLFOX), and folinic acid plus fluorouracil plus irinotecan (FOLFIRI).[210] [211] [212]

» Despite the benefits of triplet therapy, two-drug regimens are generally preferred due to lower toxicity.

» Other options for first-line therapy include docetaxel plus cisplatin; paclitaxel plus cisplatin; paclitaxel plus carboplatin; or single-agent capecitabine, fluorouracil, docetaxel, or paclitaxel.[15]

» Second-line and subsequent lines of treatments for metastatic disease are based on prior treatment and performance status.[15]

» See local specialist protocol for dosing guidelines.

plus **best supportive care**

Treatment recommended for ALL patients in selected patient group

» Patients may have symptoms secondary to the local and systemic effects of malignancy, such as dysphagia, oesophageal obstruction, pain, bleeding, and malaise, in addition to underlying comorbidities. Palliation of symptoms and maintaining quality of life is, therefore, central to managing patients with metastatic disease.

» Dysphagia and oesophageal obstruction may be relieved using palliative radiotherapy (external beam radiotherapy or brachytherapy) or self-expanding metallic stent insertion, depending on the degree of dysphagia and its impact on nutrition, quality of life, performance status, and prognosis.[15] [88][133] The National Institute for Health and Care Excellence in the UK advises against routine use of external beam radiotherapy after stent placement in patients with oesophageal cancer and recommends that it should only be used in those with oesophageal cancer having prolonged post-interventional bleeding or a known bleeding disorder. If there is complete obstruction, endoscopic lumen restoration should be performed via

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simultaneous retrograde and anterograde enteroscopy.[15] Severe obstruction should be relieved with wire-guided dilation or balloon dilation and insertion of an expandable metal stent.[15] These options should be considered for moderate obstruction, balancing the associated risks and benefits.[15] Photodynamic therapy may be effective but is less commonly used due to associated photosensitivity and costs.[15] Surgery may be useful in carefully selected patients.[15]

» Nutritional status should be optimised with dietetic input (including dietary advice, nutritional supplements, and, if appropriate, short-term enteral feeding).

adjunct **targeted therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» trastuzumab

OR

» pembrolizumab

OR

» nivolumab

OR

» nivolumab
-and-
» ipilimumab

OR

» dostarlimab

» It is important that all patients with oesophageal cancer undergo biomarker testing (e.g., for human epidermal receptor 2 [HER2], metastatic microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], and programmed death-ligand 1 [PD-L1] overexpression) to identify those suitable for targeted therapies.These agents may be used alone or in combination with chemotherapy, depending on the drug. Available preferred options include trastuzumab, nivolumab, and pembrolizumab. The preferred treatment options for MSI-H/dMMR tumours include

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pembrolizumab (alone or in combination with fluoropyrimidine- and platinum-based chemotherapy), dostarlimab, and nivolumab (in combination with ipilimumab or fluoropyrimidine- and platinum-based chemotherapy).

» Trastuzumab (an anti-HER2 monoclonal antibody) is approved for use in patients with previously untreated metastatic HER2-positive adenocarcinoma, in combination with first-line platinum- and fluoropyrimidine-based chemotherapy.[15] [114] [154] In the ToGA trial, trastuzumab combined with chemotherapy (cisplatin plus either capecitabine or fluorouracil) improved survival (16.0 vs. 11.8 months) in patients with HER2-positive oesophageal and gastric adenocarcinoma compared with chemotherapy alone.[114]

» Pembrolizumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line therapy with a fluoropyrimidine, a platinum agent, and trastuzumab for patients with HER2-positive adenocarcinoma.[15] [155] Pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy may be used for the first-line treatment of patients with squamous cell carcinoma or HER2-negative adenocarcinoma.[15] [88] [155] In Europe, this approval is limited to patients with combined positive score ≥10. In the KEYNOTE-859 study comprising patients with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma, the combination of pembrolizumab with chemotherapy has shown significant and clinically meaningful improvement in overall survival with manageable toxicity, compared with placebo.[156]

» Nivolumab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) may be added to first-line treatment with fluoropyrimidine- and platinum-based chemotherapy for patients with HER2-negative advanced oesophageal or oesophagogastric junction adenocarcinoma.[15] [155] The National Institute for Health and Care Excellence (NICE) in the UK recommends nivolumab after fluoropyrimidine and platinum-based therapy for the treatment of previously treated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma in adults.[157] NICE further recommends nivolumab plus fluoropyrimidine-based and platinum-based therapy as an option in adults with untreated

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unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma whose tumours express PD-L1 at a level of 1% or more when pembrolizumab plus chemotherapy is not found to be suitable.[158] Nivolumab is approved in combination with fluoropyrimidine- and platinum-based chemotherapy and in combination with ipilimumab for the first-line treatment of patients with advanced oesophageal squamous cell carcinoma.[15] [155]

» Dostarlimab (a PD-1-blocking monoclonal antibody [immune checkpoint inhibitor]) is approved for the treatment of patients with DNA mismatch repair-deficiency recurrent or advanced solid tumours that have progressed on or following prior treatment, who have no alternative treatment options, and who have not previously received a PD-1 or PD-L1 inhibitor.[15]

» Second-line or subsequent therapy depends on prior therapy and performance status.[15]

» See local specialist protocol for choice of regimen and dosing guidelines.

Ongoing

recurrent disease

locoregional recurrence — **1st** — **surgery or chemoradiotherapy or chemotherapy and/or palliative/best supportive care**

» Patients with locoregional recurrence that occurs subsequent to chemoradiotherapy can be considered for surgery if the tumour is resectable (depending on performance status and patient preference).

» Patients with locoregional recurrence that occurs following surgery without the use of chemoradiotherapy can be considered for chemoradiotherapy, surgery, chemotherapy, and palliative care/best supportive care (depending on performance status and patient preference).

» Patients may have symptoms secondary to the local and systemic effects of malignancy, such as dysphagia, oesophageal obstruction, pain, bleeding, and malaise, in addition to underlying comorbidities. Palliation of symptoms and maintaining quality of life is, therefore, central to managing patients with metastatic disease.

» Dysphagia and oesophageal obstruction may be relieved using palliative radiotherapy (external beam radiotherapy or brachytherapy) or self-expanding metallic stent insertion, depending on the degree of dysphagia and its impact on nutrition, quality of life, performance status, and prognosis.[15][88] [133] The National Institute for Health and Care Excellence in the UK advises against routine use of external beam radiotherapy after stent placement in patients with oesophageal cancer and recommends that it should only be used in those with oesophageal cancer having prolonged post-interventional bleeding or a known bleeding disorder.[133] If there is complete obstruction, endoscopic lumen restoration should be performed via simultaneous retrograde and anterograde enteroscopy.[15] Severe obstruction should be relieved with wire-guided dilation or balloon dilation and insertion of an expandable metal stent.[15] These options should be considered for moderate obstruction, balancing the associated risks and benefits.[15] Photodynamic therapy may be effective but is less commonly used due to associated photosensitivity and costs.[15] Surgery may be useful in carefully selected patients.[15]

Ongoing

» Nutritional status should be optimised with dietetic input (including dietary advice, nutritional supplements, and, if appropriate, short-term enteral feeding).

unresectable or metastatic recurrence — **1st** — **palliative/best supportive care**

» Patients with unresectable recurrent disease or metastatic disease that occurs following treatment can be considered for palliative/best supportive care (including systemic and targeted therapies).

» Patients may have symptoms secondary to the local and systemic effects of malignancy, such as dysphagia, oesophageal obstruction, pain, bleeding, and malaise, in addition to underlying comorbidities. Palliation of symptoms and maintaining quality of life is, therefore, central to managing patients with metastatic disease.

» Dysphagia and oesophageal obstruction may be relieved using palliative radiotherapy (external beam radiotherapy or brachytherapy) or self-expanding metallic stent insertion, depending on the degree of dysphagia and its impact on nutrition, quality of life, performance status, and prognosis.[15] [88] [133] The National Institute for Health and Care Excellence in the UK advises against routine use of external beam radiotherapy after stent placement in patients with oesophageal cancer and recommends that it should only be used in those with oesophageal cancer having prolonged post-interventional bleeding or a known bleeding disorder.[133] If there is complete obstruction, endoscopic lumen restoration should be performed via simultaneous retrograde and anterograde enteroscopy.[15] Severe obstruction should be relieved with wire-guided dilation or balloon dilation and insertion of an expandable metal stent.[15] These options should be considered for moderate obstruction, balancing the associated risks and benefits.[15] Photodynamic therapy may be effective but is less commonly used due to associated photosensitivity and costs.[15] Surgery may be useful in carefully selected patients.[15]

» Nutritional status should be optimised with dietetic input (including dietary advice, nutritional supplements, and, if appropriate, short-term enteral feeding).

Emerging

Tislelizumab

Tislelizumab is an anti-programmed cell death-1-receptor (PD-1) monoclonal antibody. It has been shown to improve overall survival compared with chemotherapy (investigator's choice of the following single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan) and is a promising second-line agent.[15][213] [214] Tislelizumab monotherapy has been approved by the US Food and Drug Administration (FDA) for adults with unresectable or metastatic oesophageal squamous cell carcinoma who have received prior systemic chemotherapy that did not include a programmed death-ligand 1 (PD-L1) inhibitor. It is approved in Europe as monotherapy for adults with unresectable, locally advanced, or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy. According to one randomised phase 3 trial, first-line treatment with tislelizumab plus chemotherapy has better overall survival with a manageable safety profile than placebo plus chemotherapy in patients with advanced oesophageal squamous cell carcinoma.[215] [216]

Bemarituzumab

Bemarituzumab is a monoclonal antibody against fibroblast growth factor receptor 2b (FGFR2b). The US FDA has granted bemarituzumab breakthrough therapy designation for the first-line treatment of patients with FGFR2b-overexpressing and HER2-negative metastatic and locally advanced gastric and oesophago-gastric adenocarcinoma in combination with modified FOLFOX6 (fluoropyrimidine, folinic acid, and oxaliplatin). In the phase 3 FIGHT trial, bemarituzumab plus FOLFOX6 demonstrated clinically significant and substantial improvements in the primary endpoint of progression-free survival compared with FOLFOX6 alone in patients with FGFR2b+, non-HER2-positive frontline advanced gastric or oesophago-gastric cancer.[217] [218]

Toripalimab

Toripalimab is an anti-PD-1 monoclonal antibody. In one phase 3 trial of patients with treatment-naive advanced oesophageal squamous cell carcinoma, toripalimab plus paclitaxel and cisplatin was associated with a significantly longer progression-free and overall survival compared with treatment with chemotherapy alone.[219] It is approved in Europe for the treatment of unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma, in combination with paclitaxel and cisplatin. It is not approved in the US for this indication as yet.

Camrelizumab

Camrelizumab is an anti-PD-1 monoclonal antibody. Treatment with camrelizumab plus chemotherapy (paclitaxel and cisplatin) was associated with longer overall and progression-free survival, compared with treatment with placebo plus chemotherapy, in one phase 3 trial of treatment-naive patients with unresectable, locally advanced or recurrent oesophageal squamous cell carcinoma.[220]

Tegafur/gimeracil/oteracil (S-1)

Tegafur/gimeracil/oteracil (S-1) is an oral prodrug of fluorouracil with a prolonged half-life. Perioperative chemotherapy with S-1 and oxaliplatin has been associated with improved 3-year disease-free survival in patients with locally advanced oesophago-gastric junction adenocarcinoma, compared with perioperative chemotherapy with capecitabine and oxaliplatin.[221] Older people may tolerate S-1 better than other chemotherapeutic agents. One phase 3 trial found that chemoradiotherapy with S-1 was associated with improved 2-year overall survival, compared with radiotherapy alone, in older patients with locally advanced or metastatic oesophageal cancer (median age 77 years).[222]

Robotic oesophagectomy

Results from a single-centre randomised trial of patients with resectable intrathoracic oesophageal cancer suggest that robot-assisted minimally invasive thoraco-laparoscopic oesophagectomy (RAMIE) reduces overall surgery-related and cardiopulmonary complications compared with open transthoracic

oesophagectomy (OTO).[223] The 5-year disease-free survival rate did not differ with surgical approach (42% in the RAMIE group and 43% in the OTO group); no statistically significant difference in recurrence rate nor recurrence pattern was observed.[224] Further research is warranted.

Iodine-125 (125-I) brachytherapy

Small observational studies suggest that 125-I seed implantation may be of some benefit in patients with lymph node metastases or recurrence.[225] [226] Further research is required.

Intensity-modulated radiotherapy (IMRT)

An advanced form of 3D conformal radiotherapy (3D-CRT) that changes the intensity of radiation in different parts of a single beam whilst the treatment is being delivered. This enables simultaneous treatment of multiple areas within the target area with different dose levels, potentially reducing cardiopulmonary toxicity. Retrospective studies comparing 3D-CRT with IMRT for patients with oesophageal cancer have shown superior dose conformity and homogeneity as well as a reduction of radiotherapy dose delivered to the lungs and heart with IMRT.[227] [228] One phase 2 trial of postoperative IMRT with concurrent chemotherapy for node-positive oesophageal squamous cell cancer showed this regimen to be safe and effective with 1-year overall survival and progression-free survival rates of 91.2% and 80.4%, respectively. There were no unexpected cases of serious adverse events or treatment-related deaths.[229] Two phase 3 trials have safely employed IMRT with concurrent chemotherapy as definitive treatment for oesophageal cancer.[230] [231] A possible disadvantage of IMRT is the prolonged time for each treatment compared with other treatment techniques.

Proton beam therapy (PBT)

A highly targeted radiotherapy technique that may limit cardiopulmonary toxicity and is associated with lower rates of postoperative complications, including pulmonary, cardiac, gastrointestinal, and wound complications, as well as reduced length of hospital stays.[232] [233] One phase 2B trial that randomised 145 patients to receive IMRT or PBT reported that PBT reduced the risk and severity of adverse events while maintaining similar rates of 3-year progression-free survival (50.8% for IMRT and 51.2% for PBT) and 3-year overall survival (44.5% for both).[234] An ongoing phase 3 study comparing PBT to photon therapy for patients with oesophageal cancer is recruiting patients.[235] National Comprehensive Cancer Network (NCCN) guidelines currently recommend that patients with oesophageal cancer should be treated with PBT within a clinical trial.[15]

Intensity-modulated proton beam therapy (IMPT)

Another emerging radiotherapy technique that uses magnets to steer the proton beam, potentially reducing toxicity to non-target tissues. Studies have shown significant reductions in mean radiotherapy dose to the heart, lungs, kidneys, liver, and small bowel.[232] [236] Clinical outcomes of IMPT for oesophageal cancer are needed, as current evidence is limited to dose comparisons.[15]

Primary prevention

Avoiding tobacco and alcohol may reduce the risk of oesophageal squamous cell carcinoma (OSCC).[80]

Diets high in cruciferous vegetables (cabbage, broccoli, cauliflower), green and yellow vegetables, and fruits are associated with a decreased risk of OSCC.[74] [75] [76]

There is evidence to suggest chemopreventive effects of aspirin and non-steroidal anti-inflammatory drugs.[80] [81] [82] Risks for harm may preclude the routine use of these agents.[83]

Statins may reduce the risk of development of oesophageal adenocarcinoma (OAC); more data are required.[84] [85] [86]

It is not known whether elimination of gastro-oesophageal reflux by surgical or medical means reduces the risk of OAC.[80]

Patient discussions

Post treatment, patients should be encouraged to consume small food portions, and consider eating smaller meals more frequently (e.g., 5 small meals each day).[15] Elevation of the head of the bed and using a triangular pillow may help to reduce nocturnal symptoms of reflux.

Discuss further measures that may be of benefit to patients experiencing long-term sequelae (e.g., gastrointestinal issues, fatigue, chemotherapy-induced neuropathy).

FOLLOW UP

Monitoring

Monitoring

Surveillance strategies after successful treatment for oesophageal cancer are controversial. Approximately 90% of relapses occur within the first 2 years after completion of local therapy.[15] Patients are generally seen on an outpatient basis 2-3 weeks after discharge. Thereafter, follow-up visits with a physical examination (which may include imaging tests, blood tests, and endoscopy) may be recommended every 3-6 months for the first 2 years after treatment.[249] Subsequent follow-up may be at 6- to 12-month intervals for the next 3 years. Follow-up visits should concentrate on symptoms, nutrition, and psychosocial support; care is often provided by a multidisciplinary team including surgeons, dieticians, radiologists, gastroenterologists, psychologists, and social workers.[88]

Due to increased risk of early recurrence, patients who have experienced complete response to definitive chemoradiotherapy should be considered for endoscopy, biopsies, and computed tomography (CT) scan at 3 months.[88]

Routine oesophageal cancer-specific surveillance is not recommended for more than 5 years following completion of treatment.[15] Annual examination and history may be considered because second primary cancers may occur.

Complications

Complications	Timeframe	Likelihood
adverse effects of immune checkpoint inhibitor therapy	**short term**	**high**
The most common adverse effects of programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor therapies are: anaemia (45.4%), fatigue (34.3%), dysphagia (30.0%), neutropenia (19.6%), lymphopenia (10.2%), hypertension (9.3%), and elevated lipase (7.2%).[245] Other potential adverse effects include colitis, myocarditis, pericarditis, and skin toxicities. Guidelines for monitoring of patients and management of complications are available.[246] [247]		
postoperative pneumonia	**short term**	**high**
This is the most common postoperative complication, occurring in as many as 25% of patients.[243] This is one of the most frequent causes of death in patients with oesophageal cancer treated by surgery.		
aspiration pneumonia	**short term**	**medium**
In patients with oesophageal obstruction, aspiration may occur.		
post-resection oesophageal reflux	**long term**	**high**
Reflux disease is considered an unavoidable consequence of oesophageal resection followed by gastric interposition. Mucosal damage from acid and bile exposure in the oesophageal remnant affects about 50% of these patients.[248]		
oesophago-aortic fistula	**long term**	**low**
This rare complication usually occurs with squamous cell carcinomas of the upper thorax, especially when they arise on the left side. They are almost always fatal but, rarely, a herald bleed may occur, thus allowing urgent surgery and graft placement.		
tracheo-oesophageal fistula	**variable**	**low**
Tracheo-oesophageal and broncho-oesophageal fistulae are severe complications, which are most likely to occur with squamous cell lesions in the mid-oesophagus. Treatment can involve either the airway or the oesophagus or both.		

Prognosis

Oesophageal cancer remains one of the most lethal of all malignancies. Without aggressive treatment, the cancer tends to obstruct the oesophagus and cause severe dysphagia. In addition to local progression causing pain, the disease tends to metastasise widely to the lungs, liver, and bone.

Survival depends on stage of disease and treatment; lymph node involvement is an important determinant of survival.[237] Favourable prognostic factors include early-stage disease and complete resection.

Based upon US data from 2011 to 2017, 5-year relative survival rates for people diagnosed with localised, regional, and distant oesophageal cancer are 46.4%, 25.6%, and 5.2%, respectively.[238] Overall 5-year survival rate (all stages of disease) is 22%.[8] Five-year survival rates for oesophageal adenocarcinoma may be slightly better than those for squamous cell carcinoma (localised stage at diagnosis 51.1% vs. 32.0%; regional 26.5% vs. 24.0%; distant 5.0% vs. 6.1%, respectively). A large pooled analysis found that women treated for oesophageal cancer had significantly improved survival versus men.[239] Chemotherapy-induced gastrointestinal toxicities were also more prevalent in women.[239]

Randomised studies demonstrate that, compared with standard trans-thoracic oesophagectomy, both minimally invasive trans-thoracic oesophagectomy and hybrid minimally invasive oesophagectomy (an Ivor Lewis procedure with laparoscopic gastric mobilisation and limited open right thoracotomy) lead to significantly lower rates of postoperative complications and accelerated recovery, without compromising survival benefit.[148] [149] One systematic review and meta-analysis reported that long-term survival following minimally invasive oesophagectomy compares favourably with, and may even be better than, open oesophagectomy in patients with oesophageal cancer.[240]

Oesophagectomy is a high-risk procedure with an incidence rate of major complications around 25% to 40%.[241] [242] One systematic review found that male sex and diabetes were prognostic factors for anastomotic leakage and major complications.[242]

Data suggest that oesophagectomy is most safely performed in high-volume units. The mortality of this procedure in such centres ranges from 2% to 6%. However, serious complications are frequent, and may occur in 20% to 40% of cases.[241] The most common complications are pulmonary disorders (10% to 50%), cardiac dysrhythmias (10%), and anastomotic leak (5% to 10%). When the anastomosis is made in the neck, a leak is rarely the cause of serious morbidity. However, dissection in the neck does carry the potential risk of temporary or even permanent recurrent laryngeal nerve injury. Average hospital stay following oesophagectomy is 10-14 days.[243] [244]

Diagnostic guidelines

United Kingdom

Oesophago-gastric cancer: assessment and management in adults (https://www.nice.org.uk/guidance/ng83)

Published by: National Institute for Health and Care Excellence **Last published:** 2023

Europe

Oesophageal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers)

Published by: European Society of Medical Oncology **Last published:** 2022

North America

NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Adverse events associated with EGD and EGD-related techniques (https://www.asge.org/home/resources/publications/guidelines)

Published by: American Society for Gastrointestinal Endoscopy **Last published:** 2022

Informed consent for GI endoscopic procedures (https://www.asge.org/home/resources/publications/guidelines)

Published by: American Society for Gastrointestinal Endoscopy **Last published:** 2022

ACR appropriateness criteria: staging and follow-up of esophageal cancer (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2022

Esophageal cancer (https://www.albertahealthservices.ca/info/cancerguidelines.aspx)

Published by: Alberta Health Services (Canada) **Last published:** 2021

Guideline on screening for esophageal adenocarcinoma in patients with chronic gastroesophageal reflux disease (https://joulecma.ca/cpg/homepage/browse-by/category/conditions/id/62)

Published by: Canadian Medical Association **Last published:** 2020

Treatment guidelines

United Kingdom

Oesophago-gastric cancer: assessment and management in adults (https://www.nice.org.uk/guidance/ng83)

Published by: National Institute for Health and Care Excellence **Last published:** 2023

Palliative photodynamic therapy for advanced oesophageal cancer (https://www.nice.org.uk/guidance/IPG206)

Published by: National Institute for Health and Care Excellence **Last published:** 2007

Europe

Oesophageal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines/gastrointestinal-cancers)

Published by: European Society of Medical Oncology **Last published:** 2022

Esophageal stenting for benign and malignant disease - update 2021 (https://www.esge.com/publications/guidelines)

Published by: European Society of Gastrointestinal Endoscopy **Last published:** 2021

North America

NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2024

The Society of Thoracic Surgeons/American Society for Radiation Oncology updated clinical practice guidelines on multimodality therapy for locally advanced cancer of the esophagus or gastroesophageal junction (https://www.practicalradonc.org/article/S1879-8500(23)00278-3/fulltext)

Published by: Society of Thoracic Surgeons/American Society for Radiation Oncology **Last published:** 2023

American Society for Gastrointestinal Endoscopy guideline on endoscopic submucosal dissection for the management of early esophageal and gastric cancers: summary and recommendations (https://www.asge.org/home/resources/publications/guidelines)

Published by: American Society for Gastrointestinal Endoscopy **Last published:** 2023

Immunotherapy and targeted therapy for advanced gastroesophageal cancer: ASCO guideline (https://old-prod.asco.org/practice-patients/guidelines)

Published by: American Society of Clinical Oncology **Last published:** 2023

NCCN clinical practice guidelines in oncology: management of immunotherapy-related toxicities (https://www.nccn.org/guidelines/category_3)

Published by: National Comprehensive Cancer Network **Last published:** 2023

ACR appropriateness criteria: staging and follow-up of oesophageal cancer (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2022

Esophageal cancer (https://www.albertahealthservices.ca/info/cancerguidelines.aspx)

Published by: Alberta Health Services (Canada) **Last published:** 2021

Treatment of locally advanced esophageal carcinoma (https://old-prod.asco.org/practice-patients/guidelines/gastrointestinal-cancer)

Published by: American Society of Clinical Oncology **Last published:** 2021

Endoscopic treatment of Barrett's esophagus with dysplasia and/or early cancer (https://gastro.org/clinical-guidance/endoscopic-treatment-of-barretts-esophagus-with-dysplasia-and-or-early-cancer)

Published by: American Gastroenterological Association **Last published:** 2019

North America

Preoperative or postoperative therapy for resectable esophageal cancer (https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/gastrointestinal)

Published by: Cancer Care Ontario **Last published:** 2016

The Society of Thoracic Surgeons practice guidelines on the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction (https://www.sts.org/resources/clinical-practice-credentialing-and-reporting-guidelines)

Published by: Society of Thoracic Surgeons **Last published:** 2014

EVIDENCE TABLES

Evidence tables

Is there randomised controlled trial evidence to support the use of preoperative chemotherapy in people with resectable thoracic oesophageal cancer?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.1076/full)

Evidence B *

Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there is a trade off between benefits and harms of the intervention.

Population: Adults with resectable thoracic oesophageal cancer
Intervention: Preoperative chemotherapy
Comparison: Surgery alone

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Overall survival (follow-up: 5 years)	Favours intervention	Moderate
Overall rate of resections	No statistically significant difference	GRADE assessment not performed for this outcome
Complete resections	Favours intervention	Moderate
Local–regional recurrence (follow-up: 5 years)	No statistically significant difference	Moderate
Distant recurrence (follow-up: 5 years)	No statistically significant difference	Moderate
Local and distant recurrence	No statistically significant difference	GRADE assessment not performed for this outcome
Response to chemotherapy	Unknown effectiveness [a]	GRADE assessment not performed for this outcome
Quality of life	Unknown effectiveness [b]	GRADE assessment not performed for this outcome
Morbidity: anastomotic leaks (follow-up 30 days) [c]	No statistically significant difference	Moderate

Note

- The Cochrane Clinical Answer (CCA) states that while there is moderate-quality evidence for overall 5-year survival and complete resections with preoperative chemotherapy, this may be offset by the risk of toxicity and possible increase in the rate of surgical complications. This is reflected in the overall rating in this table.
- The CCA also notes that caution is required when interpreting results for a variety of reasons (between-study heterogeneity; tumour histological type not being considered as a subgroup covariate; quality-of-life assessment focusing on dysphagia only).
- The Cochrane review which this CCA is based upon states that ultimately the decision to use preoperative chemotherapy should be made by the clinician and patient together and will depend on numerous factors such as survival, toxicity, quality of life, and cost of treatment.

[a] Results reported narratively (nine RCTs with 1121 people; clinical response rate ranged from 19% to 57% across studies; complete pathological response ranged from 0% to 13% across eight trials).

[b] Results reported narratively (one RCT with 802 people; reported a non-validated survey on dysphagia with 28% of participants in the chemotherapy group and 27% in the surgery group with improvement in dysphagia at one year).

[c] Morbidity was also reported for postoperative deaths and pulmonary, cardiac, gastrointestinal, and infectious complications. However, there was no statistically significant difference and GRADE assessment was not performed for any of these outcomes.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

EVIDENCE TABLES

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
- Obermannová R, Alsina M, Cervantes A, et al; ESMO Guidelines Committee. Oesophageal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022 Oct;33(10):992-1004. Full text (https://www.annalsofoncology.org/article/S0923-7534(22)01850-6/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35914638?tool=bestpractice.bmj.com)
- van Hagen P, Hulshof MC, van Lanschot JJ, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012 May 31;366(22):2074-84. Full text (https://www.nejm.org/doi/10.1056/NEJMoa1112088) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22646630?tool=bestpractice.bmj.com)
- Shapiro J, van Lanschot JJ, Hulshof MC, et al; CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015 Sep;16(9):1090-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26254683?tool=bestpractice.bmj.com)

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Images

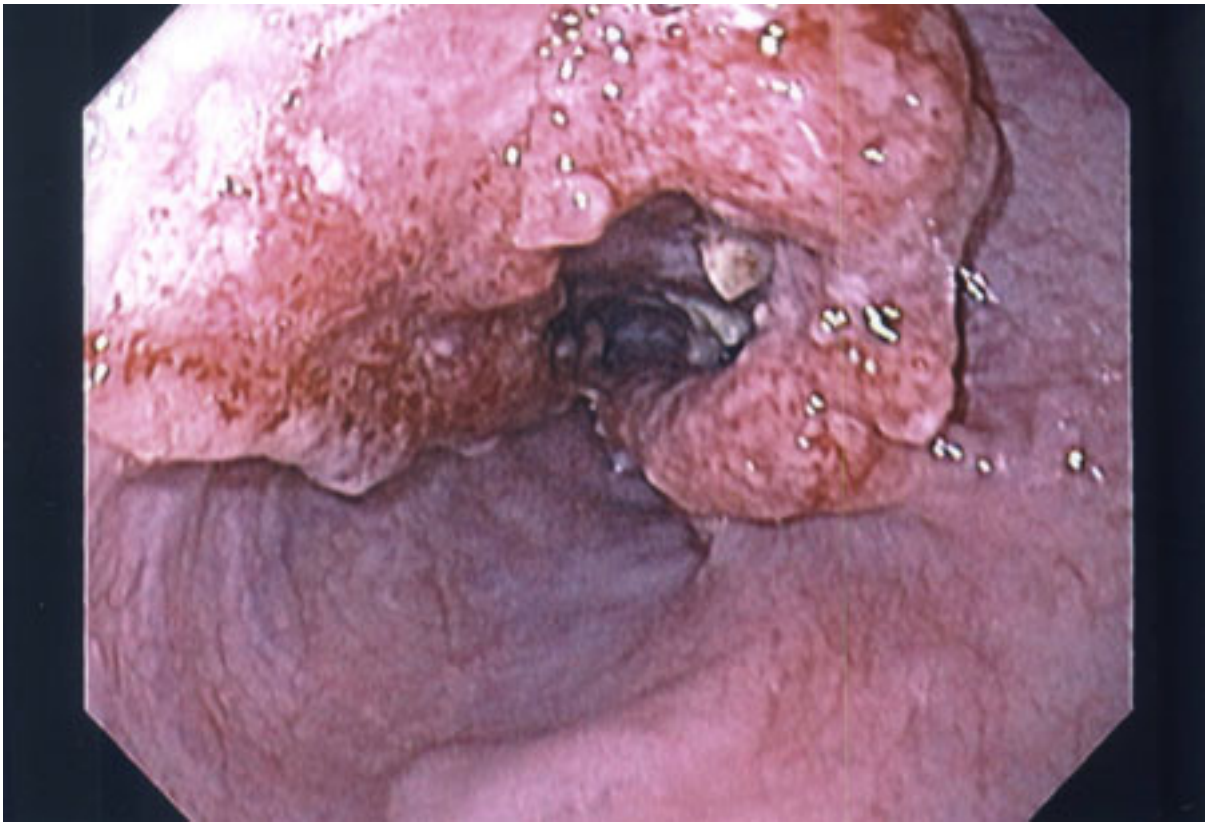

Figure 1: Endoscopic view of oesophageal cancer

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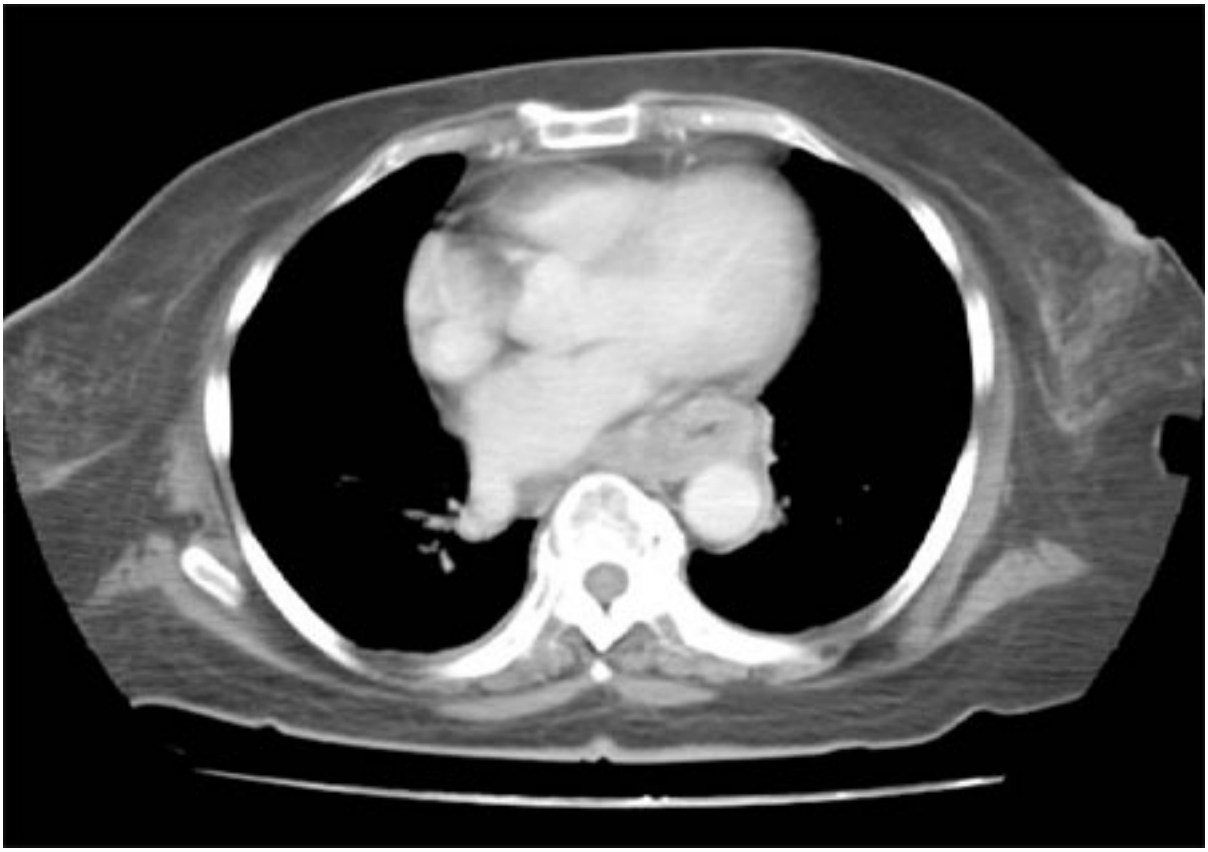

Figure 2: CT scan showing T3 tumour at level of inferior pulmonary vein

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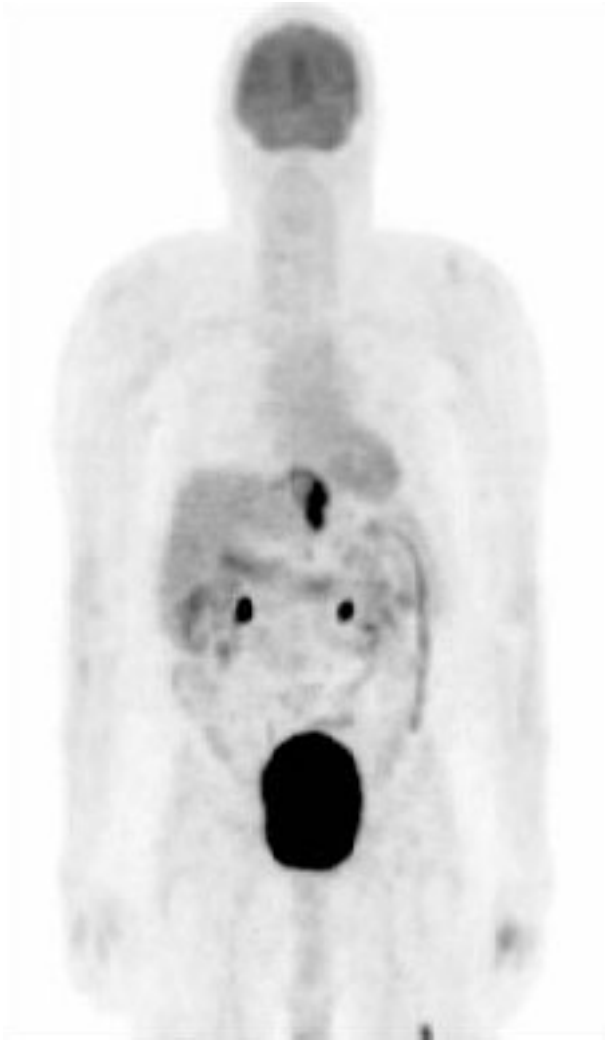

Figure 3: PET scan showing oesophageal cancer at the gastro-oesophageal junction. Note metastatic deposit in left femur

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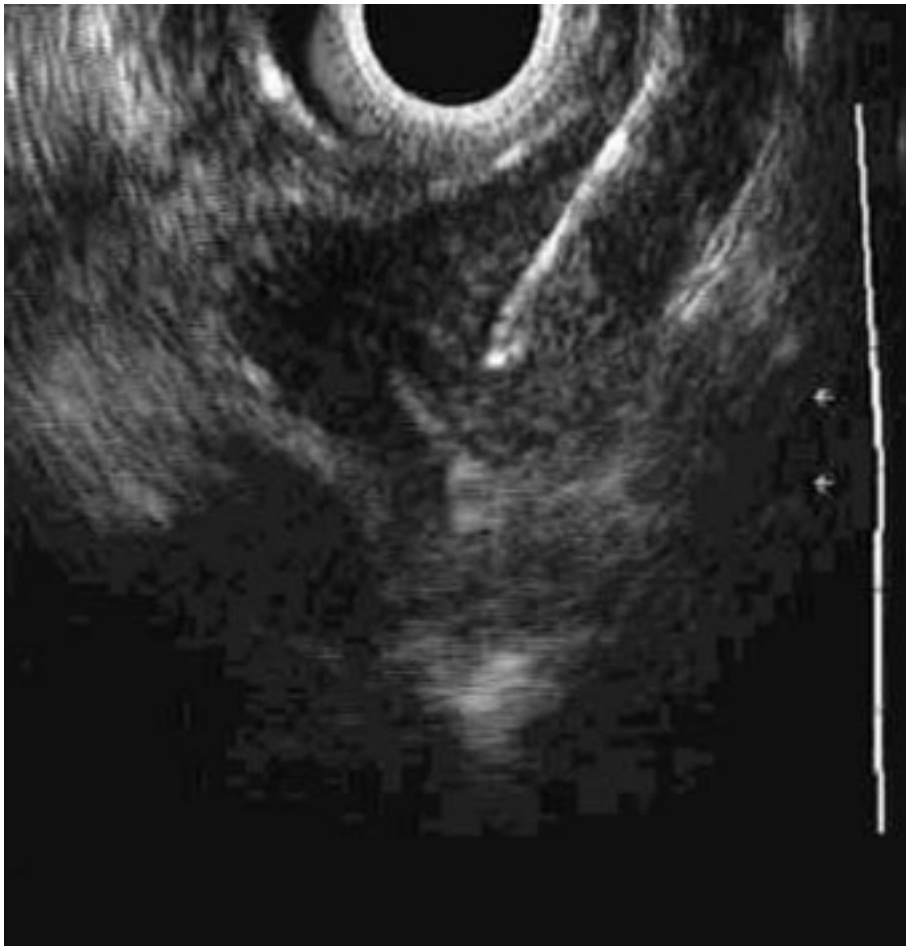

Figure 4: Endoscopic ultrasound-guided fine needle aspiration of lymph node

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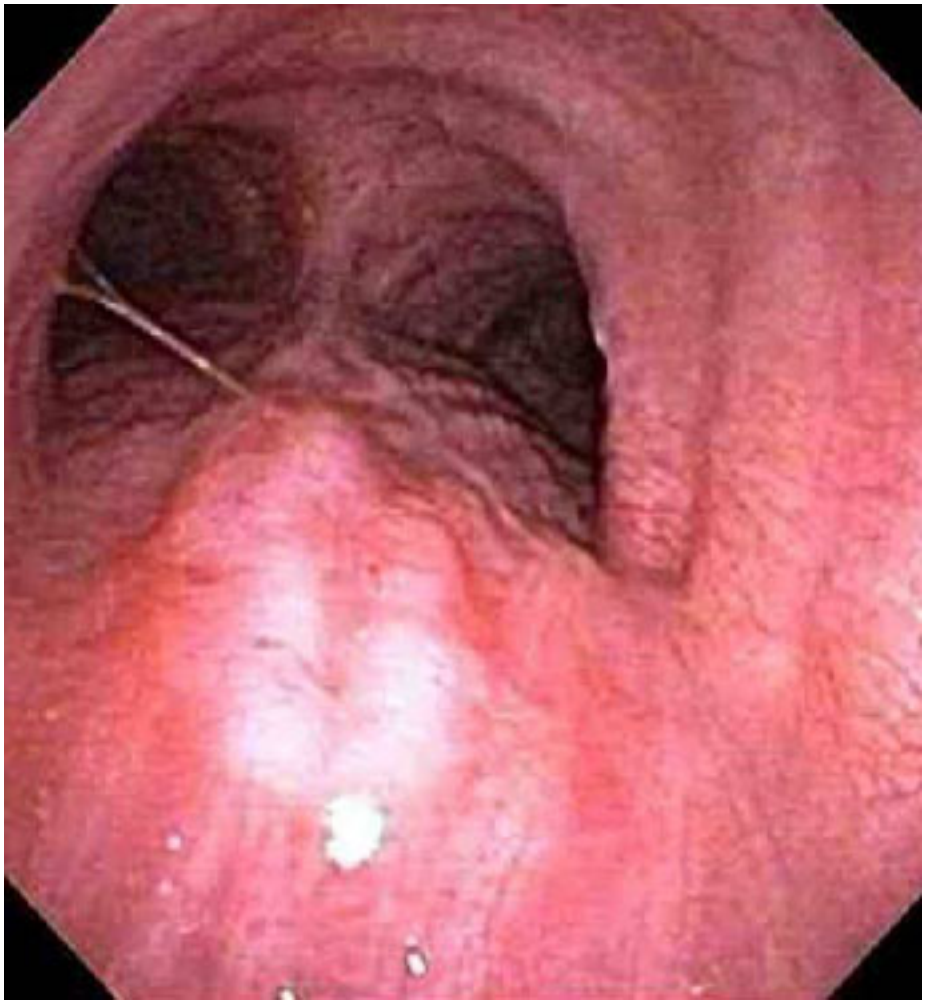

Figure 5: Tracheal invasion (T4) confirmed by bronchoscopy

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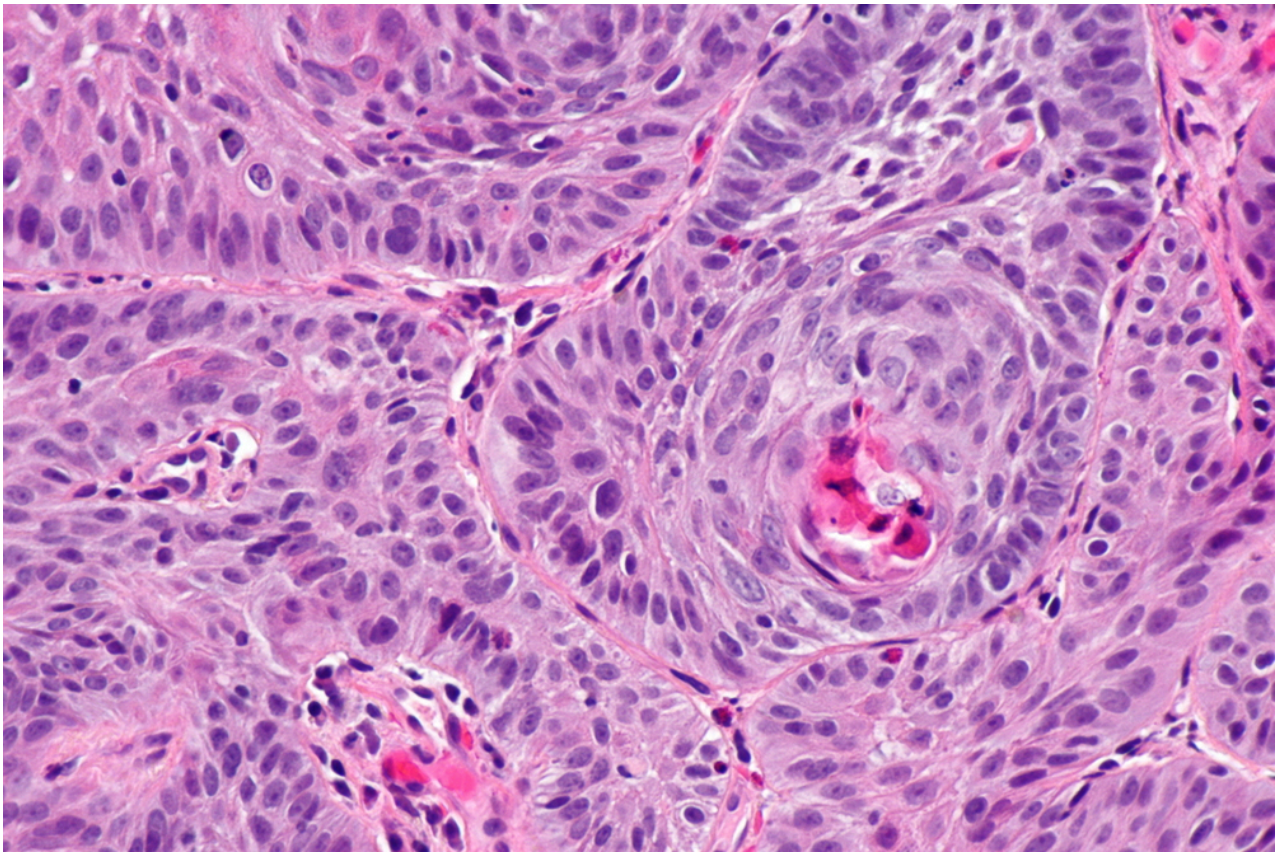

Figure 6: Moderated differentiated, keratinising oesophageal carcinoma

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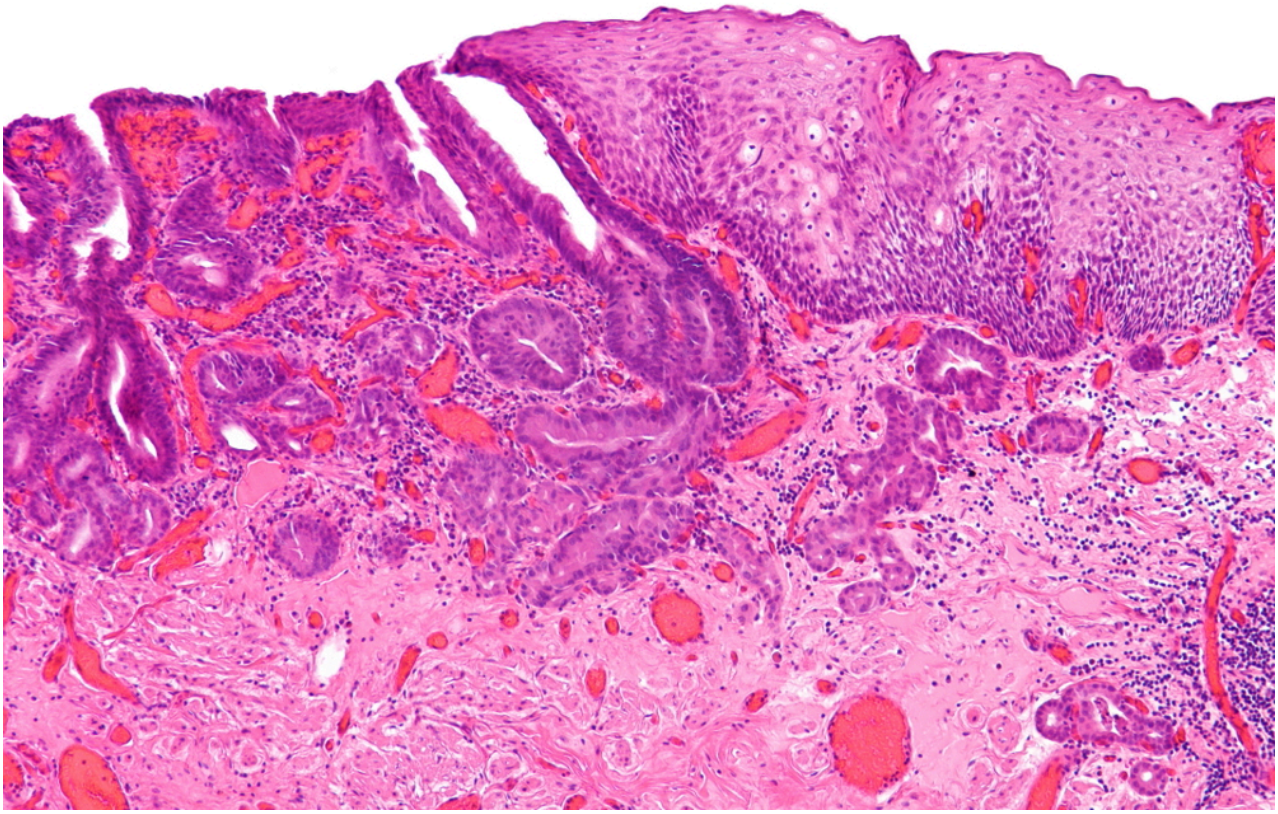

Figure 7: Adenocarcinoma (left of image) demonstrating glandular appearance with numerous mitotic cells and variable nuclear size and shape. Normal squamous epithelium is visible on the right of the image

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