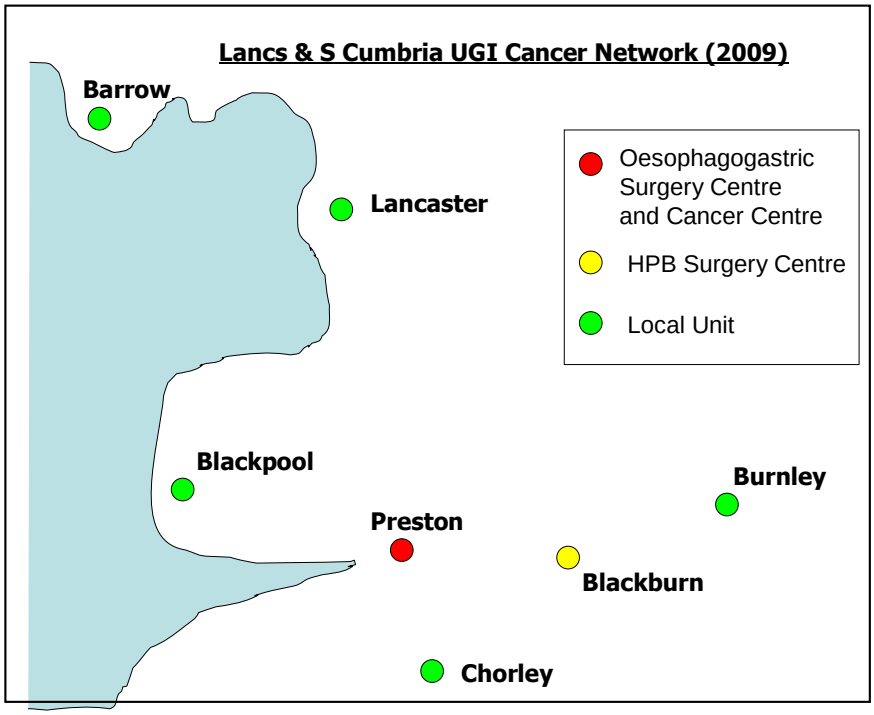
Guidelines for the management of Oesophageal and Gastric carcinoma

Lancashire and South Cumbria Upper Gastrointestinal Cancer Network



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INTRODUCTION

This document provides guidance for the management of oesophageal and gastric cancer in the Lancashire and South Cumbria Cancer Network. It has been produced with reference to guidelines published by the British Society of Gastroenterology (GUT 50: suppl v June 2002) representing a joint project between the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology, and the British Association of Surgical Oncology. The BSG guidelines were developed in response to the National Cancer Plan and aim to provide clinicians with evidence supporting best practice. The L&SCCN guidelines present this evidence but also take account of the issues of local service provision. It is recommended that they are read in conjunction with the network document "Oesophago-gastric cancer services: model of service for all patients within Lancashire and South Cumbria"

Over the past 10 years there have been significant changes in the field of oesophageal and gastric cancer. Both diseases have shown remarkable changes in epidemiology with a concentration of tumours adjacent to the oesophagogastric junction and an increase in the incidence of oesophageal adenocarcinoma such that locally this is now twice as common as squamous tumours of the oesophagus. Advances in established investigative techniques and developments in new technology have altered the way in which the two diseases can be assessed. Greater understanding of the natural history has significantly influenced the approach to diagnosis and to treatment options. Appreciation of the fundamental need for multidisciplinary treatment planning has reflected greater recognition by all interested clinicians of the role of the various treatment modalities. The essential role of best supportive care has significantly evolved emphasising the need for a holistic approach to all patients.

These guidelines have been written to highlight recent developments and to help define clinical management.

EPIDEMIOLOGY AND AETIOLOGY

Summary

- There has been a marked increase in the incidence of adenocarcinoma of the lower third of the oesophagus and gastro-oesophageal junction in the past two decades with a corresponding decrease in incidence in distal gastric cancer.
- Oesophageal and gastric cancer rates may be decreased by measures to reduce smoking and alcohol intake and to increase dietary intake of fresh fruit and vegetables.
- Oesophageal cancer may be influenced by a reduction in the duration and severity of gastro-oesophageal reflux and by a reduction in the incidence of obesity.
- Eradication of *Helicobacter* may decrease gastric cancer incidence.

Oesophageal cancer Descriptive epidemiology

Recent UK data for the mid 1990s indicate that there are an estimated 7000 new diagnoses and 6700 deaths from oesophageal cancer each year. The overall age standardised incidence has increased over recent decades especially among adenocarcinomas (ACA) close to the gastro-oesophageal junction. Data from the Office for National Statistics shows that the incidence for men and women in England and Wales is 12.6 and 5.9 per 100 000, respectively. Oesophageal cancer is essentially a disease of older age, with two thirds of cases being diagnosed over 65 years of age. The aetiology of oesophageal cancer appears to be different for each histological subtype, adenocarcinoma and squamous cell carcinoma (SCC), and independent of this for different geographical regions.

Alcohol and smoking

Case control studies suggest that, in the West, SCC is strongly related to smoking and alcohol consumption whereas in other parts of the world such as China the aetiology is more complex. In the USA the risk of both SCC and ACA is increased by both smoking and alcohol although the increase is much greater for SCC (odds ratio 16.9 *v* 3.4; 9.5 *v* 1.8, respectively). In Europe, the Americas, South Africa, northeast China, and Hong Kong, case control studies have shown a synergistic dose dependent effect of both smoking and alcohol consumption, the risks increasing substantially in those who both smoke and drink. Smokers of pipes, hand rolled, and high tar cigarettes have the highest risk among smokers.

Dietary factors

Diets lacking in vegetables, fruit, and dairy products, with low intakes of vitamins A, C, and riboflavin have been shown to predispose to oesophageal squamous cancer. Increased risk is also associated with consumption of pickled vegetables. Iron deficiency anaemia through the Paterson-Brown-Kelly syndrome is also associated with squamous carcinoma of the oesophagus. In the West, nutritional deficiency is less likely to be important in the aetiology of oesophageal cancer. ACA, perhaps through gastro-oesophageal reflux, appears strongly associated with obesity, one recent study reporting an odds ratio of 7.6 in patients with a raised body mass index.

Gastro-oesophageal reflux

Gastro-oesophageal reflux is complicated by Barrett's oesophagus in 6–14% of patients. Case control studies have shown a twofold relative risk of developing ACA of the oesophagus with reflux oesophagitis, the risk increasing with duration of symptoms, particularly in male caucasians. Recent evidence has shown that longstanding severe symptoms of reflux are associated with an increased risk of ACA, with an odds ratio of 44.

Achalasia

Achalasia predisposes to squamous carcinoma of the oesophagus. The apparent risk of cancer is highest in the first year following diagnosis, probably because prevalent cancers lead to dysphagia, prompting the initial diagnosis of achalasia. Subsequently there is a 16-fold increase in the risk of developing SCC. Patients with achalasia should be aware of the risk of oesophageal cancer. The role of endoscopic surveillance is uncertain. A population based study estimates that 406 endoscopies in males and 2220 in females would be required to detect one case of oesophageal cancer. Furthermore, there are no data to suggest that even these rates of detection would improve prognosis. However, the increased risk is a common feature of other studies and other factors including duration of symptoms and degree of food retention need to be evaluated to define high risk patients.

Primary prevention

Elimination of any aetiological factors from a population in order to try to minimise the chance of malignant transformation in the oesophagus cannot be fully achieved, as the precise sequence of events involved in the development of oesophageal cancer has not been fully elucidated. Public health education programmes should encourage reduction in smoking and avoidance of excess alcohol intake. A diet rich in fruit and vegetables should be encouraged with up to five servings per day**.** Reduction in gastro-oesophageal reflux may be achieved by suppressing gastric secretion pharmacologically or by surgery. It has not been convincingly demonstrated that such
measures might reduce the risk of oesophageal ACA, although this is the subject of an international prospective randomised study in patients with Barrett's oesophagus.

Gastric cancer: Descriptive epidemiology

Gastric cancer remains a relatively common malignancy in the UK. Recent UK data for the mid 1990s indicate that there are an estimated 10 000 new diagnoses and 7500 deaths from gastric cancer each year. The overall age standardised incidence has shown a steady decrease over the past few decades. However, this has had relatively little impact on the workload associated with gastric cancer, which has remained fairly constant, reflecting the ageing population. Data from the Office for National Statistics show that the incidence for men and women in England and Wales is 20.4 and 7.4 per 100 000, respectively. Gastric cancer is essentially a disease of older age, over 80% of cases being diagnosed after 65 years of age although a regional survey suggested that early gastric cancer (disease limited to the mucosa and submucosa) generally affects a population approximately 10 years younger than more advanced disease. In the UK, as elsewhere, the incidence of gastric cancer is strongly associated with poor socio-economic status and this largely explains the geographical pattern of disease, with higher rates in the north of England, Wales and Scotland.

Anatomical location

There has been an intriguing change in the anatomical sub-site distribution of gastric cancer, with a trend for tumours to be found more in the proximal stomach, particularly around the cardia, and a reduction in the incidence in the distal stomach. There has been an absolute increase in tumours in the cardia region and this has led to the suggestion that such cancers, along with ACA of the lower oesophagus, may be associated with gastro-oesophageal reflux.

Gastritis as an aetiological factor

Chronic inflammation of the gastric mucosa can lead to intestinal metaplasia and gastric atrophy, which are believed to be important precursors for malignant transformation. Patients with pernicious anaemia and those who have had previous gastric resection for benign disease were the first examples of this association. Over the last decade there has been increasing evidence for the role of *Helicobacter pylori* infection. This organism causes a persistent active gastritis that usually becomes chronic and may progress to atrophy. There is an increased risk of gastric cancer in *H pylori* infected individuals that has been assessed as 2–6-fold. Recent meta-analyses conclude that the risk is approximately 2.5 although this is increased for non-cardia cancers and possibly by infection with specific pathogenic strains of the bacterium. The relationship between infection and cardia cancer is currently unclear but there is a suggestion that eradication of *H pylori* may increase the risk of cardia cancer.

Dietary factors

There is much evidence to suggest that diet plays an important role in the aetiology of gastric cancer. In particular, diets containing low levels of fresh fruit and vegetable consumption increase the risk of this disease. Dietary antioxidants maybe the critical components of fruit and vegetables that are of aetiological importance. For example, in

Venezuela, Munoz and colleagues found a reduced incidence of intestinal metaplasia in populations given a diet enriched in carotene and vitamins C and E. It is also worth noting that the vitamin C content of the gastric mucosa of *H pylori* infected subjects is lower than that in healthy mucosa. A high level of salt consumption and a diet heavily dependent on preserved foods have also been postulated as important risk factors.

Smoking

As with a number of malignancies, smoking has been associated with an increased risk of gastric cancer although the magnitude of the risk is not as large as that for lung cancer.

Familial risk

Gastric cancer families have been identified and there is known to be a small (2–3-fold) elevated cancer risk imparted to first degree relatives of gastric cancer patients. This is supported by the link of germline E-cadherin mutations to some familial gastric cancers. Although this is suggestive of an inherited factor, the familial risk could also represent exposure to the same environmental influences.

Primary prevention

A diet with high intakes of fruit and vegetables (at least five servings per day) and, thereby, a satisfactory intake of antioxidants is generally appropriate health advice and likely, although not as yet proven, to reduce the incidence of gastric cancer. The increased risk of gastric cancer associated with *H. pylori* infection inevitably encourages the concept of a screening and eradication programme. It is not known however whether the mucosal changes induced by longstanding *H. pylori* infection are reversible and whether eradication will therefore influence the development of cancer.

SYMPTOMS

Summary

- The index of suspicion for cancer is high when vague dyspeptic symptoms are combined with alarm symptoms (for example, weight loss, vomiting, and anaemia). General practitioners should be encouraged to refer patients as early as possible.
- All patients with true dysphagia should be referred urgently for endoscopy or barium studies.
- Patients with a longstanding history of reflux and/or dysphagia should not be assumed to be suffering from benign stricture or simple oesophagitis until endoscopy and biopsy has been performed.

- The diagnosis of gastric cancer should be suspected in all patients with recent onset "dyspepsia" over the age of 50years as most cases of early gastric cancer do not have high risk symptoms.

Symptomatic presentation is a poor predictor of pathology as "dyspepsia" is very common. Awareness of "at risk" individuals is essential to facilitate early referral for assessment. Recent guidance for symptomatic referral from the UK Department of Health has specified the "at risk" symptoms which a general practitioner should use to seek specialist help to aid earlier diagnosis (Appendix 1). It is recommended that the specialist should see such patients within two weeks of the general practitioner deciding the patient might have cancer and making the referral. There is little data to suggest that a referral within two weeks will improve outcome quantitatively. In fact local audit suggests that the majority of 2-week referrals do not have cancer but the volume of patients referred leads to delays in diagnosis of those patients that do have cancer. Gastric cancers confined to the mucosa and submucosa have a doubling time of 1.5–10 years whereas advanced cancer has a doubling time of between two months and one year. Reducing symptomatic delay is unlikely to significantly alter prognosis for early disease but in more advanced disease a small proportion may be amenable to potentially curative surgery. Appropriate audit is required to determine if overall survival can be improved by this approach. Most studies have concentrated on early referral and ease of access for symptomatic patients. Several observational studies infer that open access endoscopy results in more cases of early stage disease, particularly gastric cancer. Other observational studies qualify this finding by highlighting the fact that open access results are heavily influenced by referral bias and that the majority of cases of gastric cancer still present at a late stage.

Symptoms: Oesophageal cancer

The principal symptom of carcinoma of the oesophagus is dysphagia. Observational studies show that cancer accounts for one quarter of all patients presenting with true dysphagia and as such all patients with this symptom should be referred urgently for endoscopy or barium studies. The increase in the incidence of ACA reflects the predominance of gastro-oesophageal reflux disease. Estimates suggest that 4–9% of adults experience daily heartburn and up to 20% experience symptoms on a weekly basis. Early assessment of such patients should be considered prior to starting empirical treatment as approximately 60% of patients with malignant disease localised to the submucosa are symptomatic at presentation. Among those with recurrent symptoms of reflux the odds ratio of developing cancer was 7.7 in comparison with those without symptoms. More frequent, more severe, and longer lasting symptoms of reflux were associated with a greater risk.

Symptoms: Early gastric cancer

Early gastric cancer is defined as ACA confined to the mucosa or submucosa, irrespective of lymph node invasion. Observational studies indicate that approximately 70% of patients with early gastric cancer have symptoms of uncomplicated dyspepsia and are not complicated by anaemia, dysphagia, or weight loss. Other studies have confirmed the benign nature of symptoms in early stage disease. Clinical diagnosis is very inaccurate in distinguishing between organic and non-organic disease and therefore all "at risk" patients

with dyspepsia should be considered for endoscopy even though the overall detection rate is only 1–2%.

Symptoms: Advanced gastric cancer
The majority of patients present with advanced disease with alarm symptoms such as weight loss, vomiting, anorexia, abdominal pain, and anaemia. In the UK, delays in diagnosis occur as a result of failure to investigate "at risk" patients with upper gastrointestinal symptoms. Such patients often have a long history of dyspepsia prior to being referred. Treatment with antisecretory therapy may also delay diagnosis or result in a misdiagnosis on first endoscopy. In particular, the ability of proton pump inhibitors to "heal" malignant ulcers has not been fully appreciated. Thus, a diagnosis needs to be established before such agents are used in "at risk" patients.

DIAGNOSIS

Summary

- **The index of suspicion for cancer is high when vague dyspeptic symptoms are combined with alarm symptoms (for example, weight loss, vomiting, and anaemia). General practitioners should be encouraged to refer patients as early as possible.**
- **Rapid access gastroscopy is the investigation of choice with appropriate biopsy for those with risk symptoms.**
- **Patients with a longstanding history of reflux and/or dysphagia should not be assumed to be suffering from benign stricture or simple oesophagitis until endoscopy and biopsy has been performed.**
- **High grade dysplasia of the oesophagus should precipitate urgent repeat endoscopy and biopsy as a significant number of patients will already have or develop intra-mucosal cancer.**
- **Antisecretory therapy should be ideally withheld until after endoscopy to avoid misdiagnosis.**
- **The diagnosis of gastric cancer should be suspected in all patients with recent onset "dyspepsia" over the age of 50 years.**
- **Gastric ulcers should be followed up to healing with repeat biopsy.**

The principal method of diagnosis in upper gastrointestinal cancer is endoscopy and the diagnosis of oesophageal and gastric cancer should always be confirmed by fibreoptic video endoscopy when barium studies have been used as the primary investigation. Rigid oesophagoscopy is no longer recommended as flexible endoscopy is safer and more cost effective. The advantages of endoscopy are that biopsies can be taken, and small lesions

evaluated more fully than is possible with radiological studies. Radiology alone will miss a high proportion of early oesophageal cancers and other pathology such as foreign body reactions can mimic neoplastic disease. However, there is very little evidence that any diagnostic procedure affects outcome. The specificity of barium studies versus primary endoscopy is similar but endoscopy allows for biopsy and cytology, which are essential for confirming the diagnosis. There are no randomised trials to show a benefit of endoscopy over barium studies, but it has been suggested that increasing the ease of investigating late onset dyspepsia could increase the proportion of early gastric cancers to 26%. Similar figures have been reported from Leeds and attributed to open access endoscopy. Other observational studies qualify this finding by highlighting the fact that open access results are heavily influenced by referral bias and that the majority of cases of gastric cancer still present at a later stage.

Barrett's oesophagus and dysplasia

The diagnosis of Barrett's oesophagus is based on a combination of visual appearance and standard biopsy specimens. Before the recognition of short and ultrashort Barrett's oesophagus, it was possible to make the diagnosis on the observation of more than 3 cm of gastric metaplasia above the gastro-oesophageal junction. Shorter segment specialised columnar epithelium is defined as intestinal metaplasia in a columnar lined segment less than 3 cm in length. Intestinal metaplasia at the cardia, which is only detectable histologically, has been referred to as "ultrashort" segment Barrett's although its malignant risk is lower as it is more likely to be associated with *H pylori* than gastro-oesophageal reflux disease. The key point for the endoscopist is thus to be able to recognise which area to biopsy. The European Society of Gastrointestinal Endoscopy has recently published minimum standard terminology in digestive endoscopy. The length of Barrett's oesophagus has been defined as the distance between the transition from oesophageal mucosa to gastric mucosa (Z-line) and the upper end of the gastric folds, the position of the Z-line being recorded in centimetres from the incisors. Thus, biopsies of this area are all important in confirming the diagnosis. High grade dysplasia warrants urgent review of endoscopy with repeat biopsy and, if confirmed, careful consideration should be given to resection as in such patient's re-evaluation will demonstrate malignant change in up to 40%. Areas of high grade dysplasia and microscopic ACA can be detected by multiple four quadrant biopsies of the oesophagus at 2 cm intervals throughout its entire length. Sampling can also be improved by taking "jumbo" biopsies of the oesophageal mucosa but even this technique may miss unsuspected Barrett's cancers. The role of surveillance endoscopy in patients with established Barrett's is controversial. Oesophageal cancers arising in Barrett's detected by surveillance are often early and have an excellent prognosis. However, studies have reported large numbers of endoscopies with little effect on diagnosis and overall survival. It remains to be established if those with risk factors such as ethnic origin, long segment metaplasia, male sex, smokers, and high alcohol intake are a more appropriate
for surveillance.

Biopsy

An endoscopic diagnosis of malignancy must be confirmed pathologically. Histology is the preferred method and the accuracy of diagnosis increases with the number of biopsies taken. Cytology can be used to complement histology but there is no evidence to show that cytology is better than biopsy alone. Indeed, as in oesophageal cancer, a positive

cytology result alone is insufficient evidence to proceed to definitive treatment for gastric cancer.

STAGING

Summary

- **Staging needs to be thorough and accurate for all patients in order to plan optimal therapy**

- **Accurate staging is achieved by a combination of techniques interpreted by dedicated staff in a timely fashion**

- **Initial staging assessment should include spiral computed tomography (CT) of the thorax and abdomen to determine the presence or absence of metastatic disease**

- **In the absence of metastatic disease, assessment of the local stage of oesophageal cancer, and thus operability, is preferably made by endoscopic ultrasound**

- **Positron emission tomography (PET-CT) is emerging as a key staging investigation in patients with cancer of the oesophagus and gastro-oesophageal junction. PET-CT can help to exclude occult metastases and characterize incidental lesions shown on conventional CT**

- **Laparoscopy is undertaken in patients with gastric cancer or cancer of the lower third of oesophagus and GOJ. Subtle peritoneal disease and small volume metastases on the liver surface undetectable by cross-sectional imaging may be found. Biopsy and peritoneal cytology can improve diagnostic accuracy**

- **Patients with middle third oesophageal cancers with no clear plane between tumour and the bronchus on CT and EUS should undergo bronchoscopy and biopsy to exclude local invasion**

- **In certain circumstances ultrasound, magnetic resonance imaging (MRI), percutaneous and peripheral node or skin biopsies may be indicated**

Rationale
Accurate staging of gastro-oesophageal tumours is needed to plan appropriate treatment. The aim is to identify patients suitable for treatment with curative intent and those with advanced disease for whom surgical exploration and radical therapies are inappropriate.

Staging objectives

- define tumour position and estimate the proximal and distal extent of the tumour and length of tumour
- identify early T1 tumours which may be suitable for local endoscopic therapies
- look for evidence of local invasion, particularly with respect to the trachea, main bronchi, aorta, pericardium, pleura, diaphragmatic hiatus and crura
- demonstrate lymph node enlargement, particularly peri-oesophageal, mediastinal and perigastric regions
- identify metastases in retroperitoneal lymph nodes, in the liver and peritoneal cavity.
- determine the degree of oesophageal obstruction and identify the presence of complications such as localised perforation or fistulation.

Methods
Accurate staging of oesophageal and gastric cancer is essential for patients wishing to be considered for and fit enough to undergo treatment. Computed tomography (CT) is the initial investigation. Endoscopic ultrasound (EUS) is done to define the 'T' stage of oesophageal and GOJ tumours and the same tumour groups are assessed by positron emission tomography (PET-CT). Laparoscopy is offered to patients with gastric cancers and tumours of the lower third of oesophagus and GOJ. This procedure can include photography, biopsy and peritoneal cytology. Bronchoscopy is used to exclude invasion of the bronchus from middle third oesophageal cancers. Finally, some patients may have magnetic resonance imaging (MRI), transabdominal ultrasound, percutaneous or open biopsies to resolve equivocal findings.

Computed tomography
Spiral contrast-enhanced scans of thorax and abdomen are available on seven sites within the Network.

Oesophageal protocol:

- Oral administration of 1 litre of water or iodinated contrast medium
- 100-150 ml of intravenous iodinated contrast medium injected at 3-4 ml/sec.
- MDCT is commenced at 20-25 seconds (chest) and 70-80 seconds (abdomen) post-injection.
- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 1.25-2.5 mm and reformatted at 5 mm for viewing.

(Values of CTDIvol should normally be below the relevant national reference dose for the region of scan and patient group)

CT cannot delineate the component layers of the oesophageal wall and therefore is unable to differentiate between T1 and T2 lesions. CT cannot detect microscopic invasion in T3 tumours and differentiating macroscopic T3 from focal tumour bulging or juxta-lesional lymphadenopathy can be impossible, particularly in cachectic individuals. Understaging is more common than over staging. CT findings suggesting T4 involvement of the aorta, tracheobronchial tree, and crura are well documented but the signs are "soft" leading to poor sensitivity when compared with EUS. However, CT can predict mediastinal invasion in over 80% of patients.

Gastric protocol:

- Oral administration of 1 litre of water as a contrast agent, of which 400 ml is to be drunk immediately prior to going onto the scanner to ensure maximum gastric distension (an anti-peristaltic agent is, in general, not required).

- Distal gastric tumours are best assessed with the patient in the prone position

- MDCT is commenced at 20-25 seconds (chest) and 70-80 seconds (abdomen and pelvis) post-injection.

- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 1.25-2.5 mm and reformatted at 5 mm for viewing.

  (Values of CTDIvol should normally be below the relevant national reference dose for the region of scan and patient group)

Adequate gastric distension is required for CT to identify the primary lesion and determine the extent of the abnormal wall thickness. Achieving this distension can be problematic in patients with advanced gastric carcinoma. CT cannot differentiate between T1 and T2 lesions. T3 lesions can be suggested by identifying stranding into the adjacent perigastric fat but differentiating between transmural extension and perigastric lymphadenopathy can be difficult. Most contemporary studies report accuracy of 80–88% in identification of patients with advanced disease. T4 diagnosis on CT relies on the presence of contact between
tumour and contiguous organs, a focal loss of intervening fat plane, or clear CT evidence of direct organ invasion. These signs may be difficult to evaluate in the cachectic patient.

Endoscopic ultrasound
EUS is offered to all patients with oesophageal and gastric cancer deemed resectable on CT staging criteria. It is a requirement for the OEO5 trial of neo-adjuvent chemotherapy. Patients with small early tumours of the oesophagus and stomach will be scanned to assess if endoscopic therapies may be considered. EUS is well established on the Blackburn site where EUS guided fine needle biopsy is also available. EUS is available in the other three Trusts and this staging modality can be offered close to home for the patient.

Oesophagus: The ability to identify the component layers of the wall of the gut provides the basis for tumour staging. EUS is superior to CT for local staging of oesophageal tumours and is more accurate in predicting resectability although the complementary nature of these imaging techniques must be emphasised. Non-traversable stenotic oesophageal tumours at initial endoscopy require dilatation, preferably under image intensification. Such tumours are highly likely to be stage T3 or greater. The 8.5 mm "blind oesophagoprobe" passed over a guidewire is useful in stenotic tumours and technological improvements have overcome limitations related to the assessment of the depth of penetration.

Stomach: EUS is superior to CT for the local staging of gastric carcinoma although the complementary nature of these imaging techniques must be emphasised. Higher frequency transducers can evaluate the subgroups of T1 and assess the suitability for endoscopic mucosal resection. The presence of direct invasion into adjacent structures (T4) can be assessed on EUS by demonstrating fixity. A potential pitfall in staging is tumour penetration through the muscularis propria extending into the greater or lesser omenta but without penetration of the overlying visceral peritoneum. The TNM classification defines this as T2. However, the omental reflections around the stomach are not clearly seen with EUS and this classification raises important issues for EUS staging of gastric carcinomas. It is sometimes impossible to know if a carcinoma has penetrated the muscularis propria into the greater or lesser omenta but not breached the visceral peritoneum beyond. As in the oesophagus, there are a smaller but significant number of non-traversable stenotic tumours that prevent a full EUS evaluation.

N staging
CT scanning: Size is the only criterion for assessment of lymph nodes and is a poor predictor of involvement, particularly in the chest, where large nodes may be reactive. The accuracy of CT diagnosis of mediastinal node involvement ranges from 38% to 70%. If nodes over 8 mm in diameter are considered abnormal in the coeliac axis, a sensitivity of 48% and a specificity of 93% is achieved.77 Identification of more distant nodal groups is of particular importance as these nodal groups may not be amenable to evaluation with EUS and will often be outside the borders of even a radical resection. The revised TNM classification has changed the classification of nodal involvement in gastric cancer. Previous classifications emphasised the importance of the distance of the involved nodes from the primary tumour. However, the current classification places emphasis on the number of involved nodes. Stage N1 refers to metastases in 1–6 regional nodes, N2 7–15 nodes, and N3 involvement of more than 15 nodes. All published papers addressing the accuracy of EUS and CT in the staging of gastric cancer utilise the "old" TNM classification. The impact of these changes on the accuracy of current imaging modalities remains to be seen. Lymph nodes are well seen on EUS and certain features have been

shown to correlate well with malignant infiltration. Nodes with well defined margins greater than 1 cm in diameter, rounded, and hypoechoic are likely to be involved. Malignant nodes unfortunately may not demonstrate all four features, and large benign reactive nodes are well recognised. EUS guided fine needle node aspiration cytology may be helpful although the limitations of a negative result must be understood. Involved coeliac axis lymph nodes suggesting M1a disease from an oesophageal primary can be readily identified. The NHS health technology assessment systematic review of endoscopic ultrasound in gastro-oesophageal cancer confirms the high accuracy of EUS for T and N staging of oesophageal and gastric cancer. Initial indications suggest that the performance for T staging at the cardia is less good. Radial probes performed better than linear probes in staging gastric cancer although in staging oesophageal cancer there was no significant difference between the two probes. Staging for metastases using EUS alone is not satisfactory. PET-CT, whilst poor for T staging, gives reliable information on the presence or absence of lymph node metastases. Unfortunately, gastric cancers are not FDG avid and PET-CT is not recommended for this tumour group

M staging

A review of 838 cases of newly diagnosed oesophageal cancers revealed that 18% have metastases at presentation; 45% of metastases were in abdominal lymph nodes and 18% in cervical lymph nodes. In addition, 35% of metastases were hepatic, 20% pulmonary, 9% bone, 5% adrenal, 2% peritoneal, and 2% cerebral. In this series, all patients with bone and brain metastases were associated with metastatic disease in the abdomen and thorax. Hence, in the absence of clinical indications, evaluation of metastatic disease should be focused on examination of the thorax and abdomen. The revised TNM classification includes some important changes relating to metastatic disease in gastro-oesophageal carcinomas. Tumours in the lower oesophagus with involved coeliac axis nodes or tumours in the upper oesophagus with involved cervical nodes are classified as M1a. Tumours of any region with other more distant metastases are classified as M1b. There is therefore "overlap" in the process between N and M staging. Spiral CT has significantly improved the detection of hepatic metastases by the introduction of techniques using thinner collimation, overlapping slices, and dual phase imaging and will detect 75–80% of metastases. However, in patients with known malignancy, only 50% of lesions less than 1.5 cm and 12% of lesions less than 1 cm are metastatic deposits. Small volume ascites can also be readily demonstrated with EUS, alerting the surgeon to the possibility of diffuse peritoneal spread. In cancers of the oesophagus and GOJ, PET-CT will identify occult metastases in the viscera, soft tissues and bone whilst lesions equivocal on CT may be clearly defined.

Laparoscopy

Peritoneal disease can be difficult to detect with conventional imaging. Laparoscopy is performed on patients with tumours in the lower third of oesophagus, gastro-oesophageal junction and stomach, deemed operable by CT and EUS and fit enough to consider surgical resection or radical chemo-radiotherapy.

Technique: Under general anaesthesia, an oblique viewing laparoscope is inserted in the epigastrium and a pneumoperitoneum is established with CO_2 insufflation. A trocar is placed in the right sub-costal area for liver retraction and another in the left sub-costal site for instruments to allow tissue manipulation, dissection and biopsy. The entire peritoneal cavity, including the lesser sac, is assessed with particular attention being paid to the

serosal aspect of the tumour, regional lymph node stations and the surface of the liver. Biopsies are taken as indicated and digital images or video clips are acquired for MDT review.

Positron Emission Tomography
PET-CT is available at Preston and is requested for all patients with oesophageal and GOJ cancer being considered for curative treatments. It is not helpful for the staging of gastric cancer. PET-CT will be done on the recommendation of the Network MDT where initial staging modalities are equivocal for metastatic lesions in distant nodes, viscera or bone. The radio-isotope 18FDG is used. Oesophageal carcinoma is intensely 18FDG avid and the technique is helpful for delineating the craniocaudal extent of oesophageal disease. Although 18FDG PET-CT can be a useful modality for the assessment of gastric carcinomas, the value of the technique in this disease appears to be less than that observed with oesophageal carcinoma. This is because the stomach often shows low to moderate grade physiological 18FDG uptake and small local involved nodes may not demonstrate significant 18FDG uptake.

Chest radiography
A chest *x* ray should only be requested in accordance with the Royal College of Radiologists guidelines and while the presence of a known malignancy suggests such a requirement, CT will be performed as part of the routine staging procedure and is far more sensitive for the detection of pulmonary metastases.

Transabdominal ultrasound
Liver ultrasound may be more appropriate than CT when there is good clinical evidence of liver metastases and treatment options are so limited that confirmation is all that is required prior to palliation. Ultrasound may also be used in conjunction with or as an alternative to MRI to help characterise indeterminate liver lesions identified using CT. Its routine use is not recommended.

Magnetic Resonance Imaging
To date there is no evidence that MR has advantages over spiral CT in T stage assessment of either oesophageal or gastric carcinoma. MR imaging of the liver may be used in specific cases such as in patients with documented allergy to intravascular contrast agents or to help characterise indeterminate liver lesions identified using CT. Reports of the use of endoluminal MR are largely laboratory based and the few clinical studies have shown no advantage over EUS.

Bronchoscopy
CT and EUS combined are highly accurate in the assessment of tracheobronchial invasion from mid and upper oesophageal tumours and bronchoscopy is not routinely required. It should however be available for use in patients where such imaging has raised suspicion but not certainty of such invasion. It provides the opportunity for biopsy and histological confirmation.

PATHOLOGY

Summary

• Diagnosis of high grade dysplasia both in Barrett's oesophagus and in the stomach should be made by an experienced histopathologist and corroborated by a pathologist with a special interest in gastro-intestinal disease.
• Reports on oesophageal resection specimens should include, as a minimum, type of tumour, depth of invasion, involvement of the resection margins, vascular invasion, the presence of Barrett's metaplasia, and the number of nodes resected and the number containing metastatic tumour.
• Reports on gastric resection specimens should include, as a minimum, type of tumour, depth of invasion, involvement of the resection margins, nodal disease (including number of involved lymph nodes), and metastatic spread.
• Oesophagogastric junctional tumours should be classified as type I (distal oesophageal), type II (cardia), and type III (proximal stomach).

Oesophageal cancer

Precursor lesions:
Oesophageal dysplasia: The presence of dysplasia in squamous epithelium suggests potential for malignant transformation. High grade dysplasia suggests malignant transformation has already occurred.

Barrett's oesophagus: Although Barrett's oesophagus is a well recognised entity, the pathological interpretation can be problematical. In essence Barrett's is characterised by three histological types:

(i) gastric fundal type epithelium with mucous secreting cells;
(ii) gastric junctional type epithelium with mucous secreting cells;
(iii) specialised columnar epithelium with mucous secreting goblet cells amounting to intestinal metaplasia.

Macroscopically, most consider columnar epithelium over 3 cm or more above the gastro-oesophageal junction as Barrett's. However, Barrett's change can also affect segments less than 3 cm and may occur with or without intestinal metaplasia. The presence of intestinal metaplasia confers the risk of malignant transformation. Endoscopically, the changes appear as an irregular edge of pink mucosa with interspersed tongues of columnar epithelium in otherwise normal pale squamous epithelium. The main significance of Barrett's oesophagus is the tendency to mucosal instability and the development of dysplasia that may progress to cancer. There is a tendency for longer segments to have a higher rate of dysplasia. Low grade dysplasia carries an increased risk of progressing to high grade dysplasia and malignant transformation. However, low grade dysplasia may undergo spontaneous regression. Indeed, there can be regression associated

with proton pump inhibitors with "healing" leaving a regenerative inflammatory atypia, which can be confused with high grade dysplasia. There are also problems with sampling error at biopsy and ensuring during endoscopic surveillance that the same area is biopsied. This is further complicated by an apparent inconsistent spatial relationship between the areas of dysplasia and areas of cancer in the same oesophagus. Such factors have led to a lack of agreement between pathologists as to the definition of dysplasia. More accurate markers are required for the loss of growth regulation in the specialised columnar epithelium of Barrett's and developments in molecular and chromosomal techniques may aid a more uniform approach.

Biopsy reporting: Biopsy specimens should be examined by an experienced histopathologist. Any unusual findings such as high grade dysplasia in Barrett's should be corroborated by a separate pathologist—a "lead pathologist" in gastrointestinal pathology. Cytological examination should be performed by an experienced cytopathologist. Unusual tumour types, although rare, may require further investigation. If possible, the presence of submucosal invasion should be identified in a biopsy specimen as this increases the likelihood of lymph node metastases.

Surgical specimen reporting: Reporting surgically resected specimens for oesophageal cancer should include the principal prognostic factors. These are detailed in the Royal College of Pathologists minimum dataset for the reporting of oesophageal tumours. Briefly, a report should include comments on the type of tumour, depth of invasion (using the TNM staging system), involvement of the resection margins, vascular invasion, and lymph node involvement. There is currently limited evidence that involvement of the circumferential resection margin indicates a worse prognosis. Where possible, involvement of this margin should be specified (separate dissection of the lymph nodes by the surgeon before sending the specimen to the pathology department may make examination of this margin impossible) There is a widespread network of lymphatic vessels in the oesophagus allowing intramural spread of tumour which may not be macroscopically evident. Satellite nodules of tumour may be very close to the proximal resection margin in spite of good macroscopic clearance.

Gastric cancer

Precursor lesions

Gastritis and intestinal metaplasia: There is now a large body of evidence to support the Correa hypothesis of a progression from chronic gastritis to gastric atrophy with intestinal metaplasia to dysplasia prior to malignant transformation. Some of the early relationships between these changes are reversible. Gastric mucosa shows atrophy with age. The relationship between the three types of intestinal metaplasia and the intestinal type of gastric cancer is at present unclear. Types 1 and 2 or complete intestinal metaplasia tend to be associated with ageing gastric atrophy and have a minimal chance of malignant transformation. Type 3 or incomplete intestinal metaplasia has a greater chance of progression to dysplasia.

Dysplasia: The grading of gastric dysplasia is subjective and open to significant interobserver variation. To simplify (from the previous mild moderate and severe

dysplasia) and to overcome this problem, low and high grade groupings are used. Patients with high grade dysplasia on more than one examination are very likely to have an ACA. However, the diagnosis of dysplasia is difficult and can be confused with regenerative changes. Consideration of referral of biopsies with severe dysplasia to a reference pathologist or pathologists should be encouraged. Reference pathologists are linked to the British Society of Gastroenterology, the Medical Research Council Gastric Planning Group, and the UK National Barrett's Oesophagus Registry.

Biopsy reporting: The majority of diagnoses are obtained from standard H and E preparations. Endoscopic biopsy can be supplemented by brush cytology. In patients with anaplastic tumours, immunocytochemical staining should be available to differentiate from lymphoma. Peritoneal washings taken at laparoscopy need to be examined cytologically and can provide valuable information about free peritoneal cells. This is significant as patients with free intraperitoneal cells have a poor prognosis with disseminated intraperitoneal recurrence and should be considered incurable by surgery alone.

Surgical specimen reporting: The principal prognostic factors for gastric ACA are the depth of penetration of the tumour and lymph node involvement. In addition, the macroscopic appearance (Borrman type), tumour location, and histological differentiation are important prognostic variables. The resection margins of the specimen need to be examined and reported. The assessment of lymph nodes should include a full dissection of the specimen to define the total lymph node number removed and the total involved by tumour. The TNM staging system73 allocates nodal stage according to the number of lymph nodes involved. Most specimens will contain a minimum of 12 nodes for examination. Malignant tumours of the stomach are usually ACA although 10% comprise lymphoma, leiomyosarcoma, and carcinoid. A range of classifications have been suggested for gastric ACA—Ming (which classifies the tumour border as being infiltrative or expansile), WHO (with a range of histopathology descriptions), Goseki (dividing tumours according to whether they have good tubal formation and intracellular mucin), and Lauren (diffuse, intestinal, and mixed types). The Lauren classification is the most widely used but only identifies a relatively small subgroup of poor prognosis gastric ACA (the diffuse carcinomas). Other factors, which have been assessed, include vascular invasion and perineural invasion. Vascular invasion is an independent prognostic variable in cardial and distal tumours. Perineural invasion is of questionable value and requires more specific definition.

Oesophagogastric junction cancers: ACA arising at the oesophagogastric junction pose many problems. They are difficult to classify as they can arise from the columnar lined lower oesophagus, from the cardia itself, or from the gastric body/fundus, with upward spread to involve the oesophagus. The surgical procedures advocated to treat these tumours remain varied and controversial. True cardia tumours behave in a more aggressive fashion than oesophageal tumours. The Japanese Society for Esophageal Disease originally classified carcinomas of the gastro-oesophageal junction as E=C, where equal parts of the tumour lie within the oesophagus and stomach, and is either EC or CE where the bulk of the tumour lies in the oesophagus and stomach, respectively. Compton and Sobin have proposed that if more than 50% of the tumour involves the stomach then it should be regarded as gastric while if more than 50% is within the

oesophagus then it should be reported as an oesophageal tumour. Those tumours of equal proportions above and below the junction are classified according to their histology and then subdivided into either oesophageal or gastric. Squamous, small cell, and undifferentiated tumour types are regarded as oesophageal while ACA (including Signet ring type) are classified as gastric. This classification is an over simplification as it does not identify true tumours of the cardia itself. Siewert and Stein have proposed a classification based on the three origins of oesophagogastric tumours mentioned above. Their type I tumour is an ACA of the distal oesophagus, the centre of the tumour lying 1–5 cm above the anatomical cardia. A type II tumour is a true carcinoma of the cardia with its centre situated between 1 cm above and 2 cm below the anatomical cardia; the type III tumour is a gastric carcinoma with its centre between 2 and 5 cm below the anatomical cardia. It is argued that these three types of tumours require different surgical approaches to ensure clear surgical margins and also because of differing patterns of lymph node metastases making the extent of lymphadenectomy different for each type of tumour. Lymphatic spread from type I lesions occurs in a cephalad direction to mediastinal nodes as well as caudally to the coeliac axis, whereas type II and III lesions metastasise almost exclusively caudally to the coeliac axis, splenic hilum, and para-aortic nodes. This classification is recommended as it is uniform, allows data comparison from different centres, and is important for the stratification of patients in prospective studies.

PRETREATMENT AND PREOPERATIVE ASSESSMENT

Summary

- **Treatment and management of all patients should be undertaken in the context of a multidisciplinary team that plans and performs staging, treatment selection (radical and palliative), treatment provision, post-treatment care, and follow up.**
- **Careful evaluation of the patient's pretreatment health must be made, particular attention being paid to the cardiovascular and respiratory systems and performance status.**
- **Quality of life at presentation should be assessed and taken into consideration in treatment planning.**
- **Routine investigations should include haematological and biochemical profiles, a resting ECG, pulmonary function tests, and exercise testing.**
- **Optimising the patient's fitness for surgery is a multidisciplinary process and all available expertise should be utilised.**
- **Patients should be encouraged to stop smoking immediately.**
- **All patients should have antithrombotic and antibiotic prophylaxis instituted at an appropriate time in relation to their surgery and postoperative recovery.**
- **Anaesthesia for oesophageal surgery should only be conducted by anaesthetists familiar with single lung ventilation and epidural analgesia.**

PRETREATMENT ASSESSMENT

Careful selection of the varying therapeutic modalities is essential. Such selection should consider not only the nature of the symptoms to be relieved but also the general medical and psychological status of the patient. Decisions should be taken in the context of the predicted prognosis and the effect of any treatment intervention on quality of life. Diagnostic work and radiological staging will be done locally at each hospital. The Trust-based multi-disciplinary teams will be in a position to identify patients with potentially operable disease and those who should not have surgery because of visceral metastases, co-morbidity or the patients' own informed choice. All patients with the diagnosis of

oesophago-gastric cancer will be included in a network-based data-base using a concise version of the Association of Upper GI Surgeons (AUGIS) data-set. All will be considered at a weekly Video-Conferenced Network MDT meeting to establish a treatment plan. Close liaison between primary care, the local MDT and the Network MDT is essential to ensure a holistic approach to patient care. Patients must be central in this process and be provided with the information they wish to have, in terms that they are able to understand, and in an efficient and timely manner. They are entitled to a detailed summary of diagnostic and staging results and the management plan recommended by the Network MDT.

PREOPERATIVE ASSESSMENT

The likely benefit derived from a particular therapy depends not only on the stage of the oesophageal or gastric disease but also on the fitness of the patient. The patient's preoperative physiological status is a major factor in determining outcome after major surgery. Although scoring systems including a variety of parameters have been evaluated, the previous medical history and concurrent morbidity remain the strongest predictors. Comprehensive preoperative evaluation and assessment of the patient is mandatory before assigning the patient to a particular therapeutic option. Where potential problems have been identified, early communication with the anaesthetic team is essential. Preoperative assessment and optimisation may necessitate a multidisciplinary approach. Only anaesthetists familiar with the complexities of single lung ventilation and epidural anaesthesia should undertake anaesthesia for esophageal surgery. In such patients perioperative invasive monitoring should be routine. Appropriate postoperative facilities for aftercare must be available prior to undertaking surgery.

Past medical history: A detailed medical history and physical examination is a prerequisite to the assessment of any anaesthetic and operative risk. Cardiorespiratory disease has been identified as the commonest coexisting disease in patients presenting for oesophagectomy. Pre-existing ischaemic heart disease, poorly controlled hypertension, and pulmonary dysfunction are all associated with increased operative morbidity, particularly in the elderly and following upper abdominal and thoracic surgery. The efficacy of any medication prescribed for cardiorespiratory conditions should be evaluated at an early stage. The American Society of Anaesthesiologists (ASA) classification of physical status is well recognised. Perioperative risk increases with increasing ASA score. Only those patients with an ASA score of 3 or less should be considered for surgery.

Social habits: Smoking is a significant aetiological factor in perioperative morbidity. All patients must be encouraged to stop smoking preoperatively.

Preoperative investigations: The minimum preoperative investigations for all patients undergoing gastric or oesophageal surgery should include baseline haematological and biochemical profiles, arterial blood gases on air, pulmonary functions tests, a resting electrocardiogram, and a chest *x* ray. Exercise capacity and testing can be informative as regards a patient's cardiorespiratory reserve. Patients with known or symptomatic ischaemic heart disease need careful evaluation, often in collaboration with specialist colleagues. More detailed investigations such as exercise electrocardiography, echocardiography, thallium imaging, and V/Q scanning may be considered appropriate in

some of these patients. Pulmonary complications are increased when the FEV1 is reduced by 20% or more. However, in evaluating pulmonary function tests consideration must be given to the fact that setting strict exclusion criteria as regards acceptable values may deny patients their only chance of curative surgery. Pulmonary function tests must be considered in relation to those appropriate for individual height and weight, the clinical findings and arterial blood gas analysis, particularly PaO2.

Preoperative preparation

Coexisting disease: All patients should be rendered optimally fit in the preoperative period before undertaking anaesthesia for gastric or oesophageal surgery. Pharmacological treatment of angina, hypertension, asthma, and COPD should be optimised. Preoperative chest physiotherapy may be beneficial. Where appropriate, haematological and biochemical abnormalities should be corrected.

Nutritional status: Patients at their ideal body weight may do better after surgery. A body mass index of less than 18.5, body weight less than 90% predicted, over 20% weight loss, and a low serum albumin are associated with an increased risk of perioperative complications. Obesity is associated with increased operative risk.

Psychological preparation: All patients should be counselled about treatment options, paying particular attention to the results and limitations of surgery. A clear description of the perioperative period should be given. An assessment of pretreatment symptoms on quality of life of the patient should be carefully undertaken as there is accumulating evidence of quality of life scores having an independent effect on outcome.

Thromboembolic prophylaxis: Appropriate measures should be taken against the risk of thromboembolic complications. Anti-thromboembolic stockings, low molecular weight heparin, and peroperative calf compression should be employed.

Perioperative management of venous thromboembolism: Venous thromboembolism (VTE) is common amongst patients having chemotherapy as part of their treatment for oesophagogastric cancer. The incidence amongst our patients is 11% and 50% of these are asymptomatic[1]. Once confirmed, treatment with therapeutic doses of Low Molecular Weight Heparin is superior to Unfractionated Heparin and Vitamin K antagonists[2]. Without anticoagulation for VTE, the risk of recurrence is 50% over 3 months; 40% in the first month and 10% during the subsequent 2 months. Therefore, patients requiring major oesophagogastric cancer resection within a month of VTE need placement of a vena-caval filter[3]. Our preference is to place a Bard Recovery Filter prior to discontinuation of anticoagulants for surgery. Surgery is carried out with the usual precautions of thromboembolism prophylaxis and therapeutic doses of LMWH recommenced as soon as is safe in the postoperative period. The filter is removed at around 12 months following insertion.

1. de Silva T, Thromboembolic complications of chemotherapy for gastro-oesophageal cancers in Lancashire and South Cumbria Cancer Network. April 2010

2. Noble SI, Shelley MD et al. Lancet Oncol 2008;9(6):577-84.

3. Guidelines on use of vena cava filters
British Committee for Standards in Haematology: Writing group: T. P. Baglin, J. Brush, M. Streiff British Journal of Haematology 2006; 134: 590-595

Antibiotic prophylaxis: Broad spectrum antibiotic prophylaxis should be administered preoperatively, or on induction of anaesthesia, in accordance with locally agreed policies
.
Blood cross match: Four units of blood should be cross matched prior to surgery. Transfusion however should be avoided if at all possible as the immunological suppressive effect can adversely affect survival.

ENDOSCOPIC MANAGEMENT OF BARRETT'S OESOPHAGUS WITH HIGH GRADE DYSPLASIA AND EARLY CANCER

Introduction

Recent NICE guidelines have made recommendations in the management of Barrett's Oesophagus (BO) with High Grade Dysplasia (HGD) and early Cancer the main points of which can be summarized below:

- Cases of BO with HGD are discussed at UGI Cancer MDT Meetings.
- Endoscopic resection (ER)/ endoscopic mucosal resection (EMR) are used for diagnosis and staging.
- ER alone can treat localised lesions:
    - HGD and BO Intramucosal (IM) Cancer T1a.
    - Some cases of BO Cancer T1b.
    - Residual and recurrent disease.
- Circumferential ER/EMR may cause stricture formation.
- Metachronous disease in the remaining BO segment may be prevented by ablative therapy following ER.
    - Radiofrequency Ablation (RFA)
    - Photodynamic Therapy (PDT)
    - Argon Plasma Coagulation (APC)
- APC, laser, Multipolar Electrocoagulation (MPEC) should not be used, alone or in combination, outside a clinical trial setting.
- Patients should be made aware of the uncertainty of long term outcome following ablative therapy, the requirement for lifelong care, surveillance and repeat endoscopy (OGD) following endoscopic therapy.

The following guidelines aim to assist Upper GI Cancer MDT decision-making in the endoscopic approach to assessment, management, and follow up of BO with HGD and/or early Cancer.

Remit

This guidance has not formally assessed the evidence for management of HGD in non-BO or early Squamous Cell Carcinoma of the Oesophagus however the techniques described are likely to be useful in these areas.

The following areas lie outside the remit of this guidance: the role of endoscopic surveillance for BO; routine surveillance for BO; assessment and management of more advanced BO Cancer.

Diagnosis

- A diagnosis of BO is made when the appearance of columnar-lined oesophagus is identified above the gastro-oesophageal junction (GOJ) at OGD with biopsies showing glandular metaplasia.
- Histological corroboration requires accurate identification of the site at which biopsies are taken (1). For example, intestinal metaplasia is consistent with a diagnosis of BO but can be present in biopsies taken from a hiatus hernia or the cardia where fundic and cardia-type mucosa is found.
- The GOJ is defined as the top of gastric folds or sphincter 'pinch' (Appendix V)

Endoscopic assessment

- All patients with BO HGD or early Cancer should have a detailed endoscopic assessment.
- After initial survey of the foregut, on withdrawal of the endoscope and decompression of the stomach, BO is recorded according to the Prague C and M criteria (2) (Appendix V).
- Conventional white light endoscopy (WLE) is the most readily available modality to make assessments.
- Mucolytic agents e.g. N-Acetyl Cysteine (1%) improve visibility.
- Acetic acid (e.g. 50:50 vinegar: water) via spray catheter highlights lesions.
- Suspected lesions should be recorded using the Paris classification (3).

Protruding		
	Pedunculated	0-Ip
	Sessile	0-Is
Non-protruding and non-excavated		
	Slightly elevated	0-IIa
	Completely flat	0-IIb
	Slightly depressed	0-IIc
	Elevated and depressed	0-IIc and IIa
		0-IIa and IIc
Excavated		
	Ulcer	0-III
	Excavated and depressed types	0-IIc and III
		0-III and IIc

- In future trimodal imaging (high resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI)) may be the recommended modality.

Histological assessment

- Surveillance.
    - Blind biopsies: the Cleveland approach, conventional biopsy forceps, 4 quadrants at 2 cm intervals commencing 1 cm above the GOJ (Appendix V).
    - Focal areas: targeted biopsies taken from any abnormal areas.
    - Biopsies: blind and targeted are identified by level (Appendix V).

    - Samples indefinite for dysplasia: repeat OGD and biopsy after 8 weeks PPI therapy, consider immunohistochemical staining with p53.
- ER/EMR specimens: flatten out and pinned out on cork, deep margins define T stage, lateral margin defines completeness of excision and need for further ER.

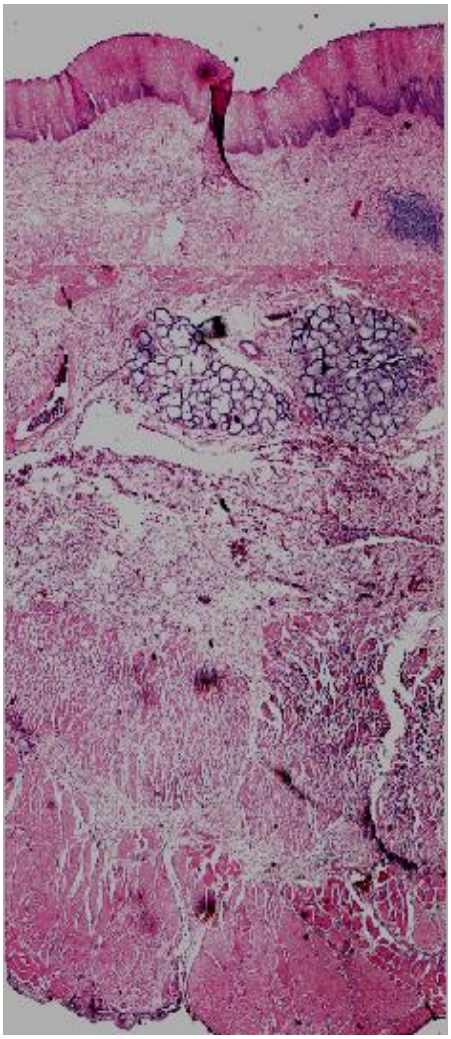
Staging of early BO Cancer

- T stage.
    - ER/EMR histology defines stage.
    - EUS is generally unhelpful.
- N and M stage.
    - EUS defines N stage in advanced Oesophageal Cancer but its value in early disease may be questioned (4).
    - Distant metastases are negligible in HGD and T1m1-3 Cancers (5, 6).
    - Early BO Cancer lymph node metastasis incidence:
        T1m1-m3 – negligible.
        T1sm1 – 0-8%.
        T1sm2-sm3 – 26-27%.
- Recommendation:

EUS and CT	**Indicated**	**Not indicated**
Paris	>0-IIc, a/c, b/c	<0-IIc
Histology	>T1sm1 Cancer	T1m1-3 Cancer
	Poor differentiation	
	Lymph vascular invasion	

Therapeutic techniques

	T stage	Depth of effect
Epithelium	T1m1	
Lamina propria	T1m2	RFA
Muscularis mucosa		
Submucosa	T1sm1	
	T1sm2	EMR
	T1sm3	EMR
Muscularis propria		PDT



ER.

EMR

	Multiband ligator	Cap
Technique	Diathermy snare tip to demarcate with margin at 4 sites	
	'Suck and diathermy snare'	'Inject, suck and diathermy snare'
Size of cap	1 cm	1.5 cm
Indication	<1 cm lesions	>1cm lesions
	Widespread flat lesion	Large area
	multiple lesions	multiple lesions

ESD

Technique	Demarcate with margin, diathermy snare, injection, cut with knife.
Indication	Very large lesions
Comments	Prolonged procedure, demanding, complications: perforation, haemorrhage, well performed piecemeal ER may be the best form of ER in very large lesions.

Ablation.

RFA

- Aim: to destroy BO segment epithelium and allow squamous re-epithelialisation.
- Technique: RFA uses radiofrequency energy via a balloon to ablate 0.5-1 mm depth of mucosa, to the level of the muscularis mucosa, in the oesophagus.
- Procedure (Appendix VI)
- Indications:

  Flat HGD: focal or diffuse
  Recurrent disease in HGD and/or T1m1-2 Cancer
  Prevention of metachronous disease in HGD and/or T1m1-2 Cancer
  In the context of a clinical research trial:
  BO with low grade dysplasia
  BO without dysplasia
- Contraindications:

  Varices
  Radiotherapy
  PDT
  APC/MPEC
  Pregnancy
  Eosinophilic oesophagitis
  Heller myotomy

PDT

- Aim: destroys BO segment to depth of muscularis propria.
- Technique: a photosensitizing agent, administered by intravenous injection, is activated by light applied locally by laser. Highly reactive singlet Oxygen, released as a consequence of the energy absorbed by the agent, leads to photochemically-induced tissue damage via apoptosis and necrosis of vascular endothelium.
- Indications: consider as alternative treatment in >T1m2 unfit for surgery.
- Adverse events: death; photosensitivity; stricture; acute neuropathy; chest pain; low-grade fever; oesophageal or lung perforation; nausea; atrial fibrillation; congestive cardiac failure; skin reaction.

APC

- Technique: non-contact energy delivered to mucosa.
- Indication: focal residual areas following ER and RFA.

MPEC

- Technique: contact thermal energy to mucosa.
- Indication: focal residual areas following ER and RFA, evidence limited.

Cryotherapy: early experience only.

Management algorithm for HGD and early BO cancer (Appendix VII)

Surveillance following endoscopic therapy (Appendix VII)

- Lifelong surveillance OGD and biopsy.
- High dose PPI long term.
- Residual symptoms consider H2 antagonist +/- Sucralfate.

Administrative support:

Staffing and infrastructure to be made available to support the following:

- Data collection for the Cancer Network
- Audit
- Research

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GUIDELINES AND FURTHER READING

Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. British Society of Gastroenterology Guidelines 2005.

NICE guidelines: IPG344 Epithelial radiofrequency ablation for Barrett's oesophagus: guidance; audit support; consultee comments; interventional procedure overview.

NICE guidelines: IPG200 photodynamic therapy for early oesophageal cancer: guidance; consultee comments; interventional procedure overview.

NICE guidelines: IPG350 photodynamic therapy for Barrett's oesophagus; guidance; consultee comments; interventional procedure overview.

History, molecular mechanisms, and endoscopic treatment of Barrett's Esophagus. Spechler SJ, Fitzgerald RC, Prasad GA, Wang KL. Gastroenterology 2010; 138: 854-69

Risk and reason in Barrett's Esophagus. Shaheen NJ. Gastroenterology 2010; 8: 233-4.

INFORMATION FOR PATIENTS

IPG344 Epitheial radiofrequency ablation for Barrett's oesophagus: guidance. understanding NICE guidance.

IPG200 Treatment of early-stage oesophageal cancer with photodynamic therapy: understanding NICE guidance.

IPG350 Photodynamic therapy for Barrett's oesophagus; understanding NICE guidance.

CARDIO-OESOPHAGECTOMY

- for oesophageal and junctional cancers
- radical excision with three field nodal clearance and >5cm proximal resection margin and > 2cm distal resection margin where possible
- cuff of diaphragm and resection of mediastinal pleura to maximize circumferential resection margin (CRM) clearance
- pyloroplasty is our preference to prevent gastric stasis and improve gastric emptying
- feeding jejunostomy placement is undertaken selectively when nutritional state is sub-optimal, or recovery is likely to be prolonged
- Thoracic epidural, single lung ventilation and level 2 observation in the early post-operative period are part of the standard protocol of care

Surgical approach:

1. Open 2-stage cardio-oesophagectomy (Ivor Lewis):
    - Rooftop incision for abdominal mobilization of the stomach, hiatal dissection and pyloroplasty
    - Right thoracotomy through 5th intercostal space for mediastinal and sub-carinal dissection with division of the azygous vein and ligation of the thoracic duct
2. Hybrid laparoscopic / open cardio-oesophagectomy
    - Laparoscopic abdominal phase
    - Open thoracic phase
    - Recruitment to ROMIO trial where possible
3. Robotic-assisted three stage cardio-oesophagectomy
    - Open abdominal phase

- Synchronous Robotic-assisted thoracic phase (Da-Vinci Xi – Intuitive Surgical Inc.)
- Open left neck exploration and oesophago-gastric anastomosis
- The favoured approach following neoadjuvant chemoradiotherapy to maximize clearance of the radiotherapy field

GASTRECTOMY

- for gastric cancers not involving the gastro-oesophageal junction
- radical excision with D2 nodal dissection: perigastric D1 nodes plus left gastric, common hepatic, splenic and coeliac nodes when appropriate
- full omentectomy
- excision of pre-pancreatic peritoneum for posterior tumours with serosal involvement
- division of duodenum at least 2cm distal to pylorus
- oesophagojejunostomy with retrocolic Roux-en-Y reconstruction
- "extended" gastrectomy including several centimetres of oesophagus may be appropriate for gastric cancers approaching the GOJ in order to maximize proximal clearance

SUB-TOTAL GASTRECTOMY

- for distal gastric cancer
- redical excision with D2 nodal dissection as for total gastrectomy
- inclusion of left gastric pedicle but preservation of short gastric vessels
- Roux loop anastomosed to gastric pouch of cardia and fundus

Surgical approach:

1. Open resection via rooftop incision

- Omnitract lifting of the costal margin
- Mobilization left lobe liver
- Pack behind the spleen to facilitate dissection of splenic hilum
- Stapled anastomoses with monofilament suture support
- Placement of feeding jejunostomy when deemed necessary

2. Laparoscopic assisted gastrectomy
    - This approach may be considered for early stage cancers and in patients with impaired respiratory function
    - The surgical procedure is identical to the open procedure and small laparotomy is commonly performed for retrieval of the specimen and construction of anastomoses

ADJUVANT TREATMENT

Oesophageal cancer

- **There is no evidence to support the use of adjuvant chemotherapy in oesophageal cancer.**
- **Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil (5-FU) improves short term survival over surgery alone.**
- **There is no evidence to support the use of preoperative radiotherapy in oesophageal cancer.**
- **Preoperative chemoradiation may improve long term survival.**
- **Chemoradiation is the definitive treatment of choice for localised squamous cell carcinoma of the proximal oesophagus.**

Gastric cancer

- **5-FU is the most active chemotherapeutic agent. A combination of 5-FU with other agents is superior to single agent treatment. The combination of epirubicin, cisplatin, and continuous infusion of 5-FU (ECF) appears to be one of the most active regimens. A recently published trial of perioperative ECF (MAGIC) has shown a 13% survival advantage at 5 years and this therapy should be considered in appropriate cases.**
- **Adjuvant chemoradiotherapy is currently not standard practice for resected gastric cancer and should be offered only within the setting of a clinical trial.**
- **Intraperitoneal chemotherapy remains investigational.**

- **Neoadjuvant chemotherapy remains investigational with no definite evidence of survival benefit and clinical trials are continuing.**

Oesophageal cancer

Adjuvant chemotherapy: The use of postoperative chemotherapy in oesophageal disease is problematical given the recovery period that commonly follows oesophagectomy. This delay conflicts with the aims of adjuvant therapy. Evidence regarding postoperative therapy is limited. A randomised trial of two cycles of postoperative cisplatin and vindesine versus surgery alone in 205 patients showed no significant difference in survival. In a subsequent study using cisplatin and 5-FU in 242 patients, there was an effect on disease free five year survival but there was no overall five year survival benefit (surgery 51% *v* surgery/ chemotherapy 61%; p=0.3). There is therefore no evidence to use adjuvant chemotherapy outside the setting of a clinical trial.

Neoadjuvant chemotherapy: An initial randomised trial of pre and postoperative cisplatin and 5-FU versus surgery alone demonstrated no benefit from the addition of chemotherapy. However, very few patients actually received the full course of chemotherapy allocated in this study. A second multicentre randomised trial including 802 patients compared two cycles of preoperative cisplatin and 5-FU with surgery alone. This demonstrated a statistically significant survival benefit for the chemotherapy treated group (median survival 530 days v 408 days; p=0.002). Furthermore, there was no difference between the two arms in the number of perioperative deaths or the rate of postoperative complications (unpublished data from the UK Medical Research Council OEO2 Trial). These results argue in favour of preoperative chemotherapy for all patients with operable oesophageal cancer other than those with unequivocally T1 tumours. This is the preferred practice locally.

Preoperative radiotherapy: A meta-analysis of five randomised trials comparing preoperative radiotherapy with surgery alone failed to detect a significant benefit of radiotherapy (hazard ratio 0.89; 95% confidence interval (CI) 0.78–1.01; p=0.062).

Neoadjuvant chemoradiation: Five randomised trials have compared chemoradiation and surgery with surgery alone in operable carcinoma of the Guidelines for the management of oesophageal and gastric cancer oesophagus (irrespective of histology). Three of these trials have not shown a survival advantage for preoperative chemoradiation but may be criticised on the basis of inadequate chemotherapy or radiotherapy doses. Chemotherapy and radiotherapy were also administered sequentially rather than concurrently in one trial. The two positive studies used chemoradiation protocols incorporating cisplatin and 5-FU, with concurrent 40 or 45 Gy radiotherapy. A meta-analysis of the five trials showed an overall improvement in three year survival from 22% with surgery alone to 31% with preoperative chemoradiation. The odds ratio for survival in favour of chemoradiation was 1.62 (95% CI 1.17–2.26). Current interest is focusing on the development of more effective combination regimens using newer chemotherapeutic agents such as the taxanes together with cisplatin and 5-FU, administering continuous low doses of cytotoxic agents

throughout radiotherapy, and delivering radiotherapy in hyper-fractionated twice daily schedules.

Definitive chemoradiation for localised SCC:

SCC typically presents in the proximal oesophagus and therefore represents a greater surgical challenge than the typical ACA of the lower third. Furthermore, patients often present at an advanced age, and may be poor surgical candidates. In non-randomised comparisons concurrent chemoradiation has produced pathological complete response rates consistently above 20% in those who went on to have subsequent surgery. The median survival for patients treated with chemoradiation is similar to those treated with surgery alone. Chemoradiation and surgery thus appear equivalent modalities in SCC of the proximal oesophagus.

Gastric and oesophagogastric junction cancer

Adjuvant chemotherapy: The rationale that postoperative chemotherapy may improve local and systemic control and ultimately survival has been under investigation for 25 years. A meta analysis of randomised trials has failed to show a benefit for chemotherapy over surgery alone (odds ratio 0.88 (95% CI 0.78– 1.08)). However, subsequent inclusion of a further two studies did suggest advantage, although the exclusion of a strongly positive study would have suggested no benefit. A recent updated meta-analysis including recent randomised trials, suggests a small survival advantage with an odds ratio for death in the treated group of 0.80 (95% CI 0.67–0.97) and a relative risk of 0.94 (0.88–1.01). None the less, there remains insufficient evidence to indicate that adjuvant chemotherapy is standard treatment and inclusion of these patients in clinical trials should continue, particularly with more effective drug regimens.

Adjuvant intraperitoneal chemotherapy: A small randomised study reported improved survival after intraperitoneal administration of mitomycin C absorbed activated charcoal after gastrectomy in T3/4 tumours. However, when repeated in a randomised multicentre trial this result was not reproduced. Intraperitoneal chemotherapy (cisplatin/5-FU) may alter the intraperitoneal failure pattern and this may enhance outcome after preoperative systemic chemotherapy. In a non-randomised trial, intraperitoneal chemotherapy post resection following neoadjuvant chemotherapy decreased recurrence rates and improved survival compared with controls. Similar results have been reported in a randomised study with the effect most marked in stage III cancers. This approach requires further evaluation and remains investigational.

Neoadjuvant chemotherapy: Although a number of non-randomised studies have suggested a benefit with improved survival compared with historical controls, randomised trial evidence is not supportive. A Korean randomised trial comparing preoperative cisplatinum, etoposide, and 5-FU with surgery alone failed to show a survival benefit although resectability was improved. A recently reported randomised study of preoperative FAMTX (5 FU, adriamycin, and methotrexate) compared with surgery alone in 56 patients found no benefit with chemotherapy. Ongoing randomised studies with

more effective regimens need to be completed to define the role of neoadjuvant chemotherapy.

Adjuvant chemoradiotherapy: The role of postoperative chemoradiotherapy in gastric cancer has recently been evaluated in a randomised trial involving 603 patients. At 3.3 years median follow up there was a disease free and overall survival advantage for the treated group. This approach needs further evaluation to determine whether this early benefit is durable.

PALLIATIVE TREATMENT OF OESOPHAGEAL CANCER

Summary

- **Palliative treatment should be planned by the multidisciplinary team with direct involvement of the palliative care team and the clinical nurse specialist.**
- **Dilatation alone should be reserved for patients who are considered to have an extremely short life span (four weeks or less) and unable to swallow saliva, or as a very short term measure to relieve dysphagia while more definitive treatment is planned.**
- **Injection of tumour with 0.5–1 ml aliquots of 100% alcohol should be considered in the following situations:**
  (a) For eccentric or soft exophytic tumours, unsuitable for endoscopic intubation.
  (b) Tumours too close to the cricopharyngeus for endoscopic intubation.
  (c) For treatment of tumour overgrowth at the ends of an oesophageal prosthesis.
- **Oesophageal intubation is the treatment of choice for firm stenosing tumours (capable of retaining an endoprosthesis), more than 2cm from the cricopharyngeus, where rapid relief of dysphagia in a one stage procedure is desirable.**
- **Expandable metal stents are preferable to plastic tubes in view of the lower complication rate at insertion and shorter hospital stay.**
- **Covered expandable metal stents or cuffed plastic tubes are the treatment of choice for malignant tracheoesophageal fistulation or following oesophageal perforation sustained during dilatation of a malignant stricture.**
- **Laser treatment is effective for relief of dysphagia in exophytic tumours of the oesophagus and gastric cardia and in treating tumour overgrowth following intubation.**
- **For patients whose dysphagia is palliated using laser therapy, the effect can be prolonged substantially by using adjunctive external beam radiotherapy or brachytherapy.**
- **Chemoradiation provides a survival benefit over radiotherapy alone.**
- **Radiotherapy or chemotherapy alone palliates dysphagia more slowly than intubation or laser treatment.**
- **Both photodynamic therapy (PDT) and argon plasma coagulation (APC) are experimental and their use is not currently recommended; there may be a role for APC in treating tumour overgrowth of stents.**

The high proportion of patients presenting with advanced disease highlights the fundamental importance of palliative treatment in oesophageal and gastric cancer. Such a

principle equally applies to patients with otherwise operable disease who are either unsuitable or unfit for radical intervention. These patients require as careful consideration by the specialist multidisciplinary team as those with potentially curable disease. Furthermore, close liaison between primary and secondary care is essential bearing in mind the short duration of life expectancy after diagnosis.

Palliative chemotherapy and radiotherapy

Dysphagia is the predominant symptom in advanced oesophageal carcinoma, and the principal goal of palliation is restoration of swallowing. Such a benefit has been shown to correlate strongly with quality of life. A variety of means may be employed to achieve this goal. Given the short lifespan following treatment, it is important that the chosen method provides rapid resolution of symptoms with minimum disruption to the patient's life and as prolonged a duration of symptom control as possible. The choice of treatment must be tailored to the individual, and will depend on the site, length, and appearance of the tumour, as well as the physical condition of the patient.

Chemoradiation for locally advanced disease: Randomised trials comparing chemoradiation with radiotherapy alone have shown a benefit in terms of response rate and survival for the combined modality arm. In the Radiation Therapy Oncology Treatment Group study, 129 patients were randomised to receive chemoradiation or radiotherapy only. Complete response rates were reported as 73% in the combined modality group and 60% in the radiotherapy alone group. Median survival was also significantly improved (12.5 v 8.9 months; p=0.009). The interim results of a trial comparing radiotherapy alone with chemoradiation reported that median survival was significantly improved in the chemoradiation arm (14.9 v 9.0 months; p=0.03).

Palliative chemotherapy: In advanced oesophageal ACA, palliative chemotherapy has the same benefit as in advanced tumours of the oesophagogastric junction or stomach. Regimens used frequently include cisplatin and 5-FU. Addition of epirubicin may improve the palliative benefit with a reduction in repeat laser requirements. A similar benefit is achievable in squamous carcinoma. Early results with paclitaxel, which is also a radiosensitiser, show response rates of 48–70% in combination with cisplatin, with or without 5-FU, including 12–23% complete response. Such responses are similar irrespective of tumour type. The use of paclitaxel should remain in the setting of clinical trials and further results, including survival and quality of life figures, are awaited.

Palliative radiotherapy or chemotherapy as stand alone treatment: Palliative radiotherapy improves dysphagia in 50–85% of patients and pain is also significantly lessened. The time to onset of improvement however is slow and improvement is more likely in patients with milder dysphagia. In a retrospective analysis of patients who received radiotherapy, chemotherapy, or a stent, median time to improvement in symptoms was two months after radiotherapy, variable but prolonged after chemotherapy, and immediate after stent insertion. Addition of brachytherapy to external beam radiotherapy induces more rapid relief of dysphagia but with a risk of serious side effects including fistula formation. It is also slower and less successful than either intubation or laser therapy.

Endoscopic therapy

Oesophageal dilatation: Improvement in dysphagia has been demonstrated in up to 70% of patients where a guide wire could be passed. The incidence of complications, including haemorrhage and perforation, is 2.5–10%. Different types of dilator have not been compared in randomised controlled trials and reported success and complication rates with balloon, Maloney, and Savary-Gillard dilators are similar. Recurrence of dysphagia occurred in a mean of 11.5 days in one case series while Lundell and colleagues reported that the procedure had to be repeated at intervals of four weeks. As a result, most clinicians reserve dilatation for patients with an extremely short life expectancy.

Injection therapy: Intratumoral injection of absolute alcohol is of value in soft exophytic tumours and tumours situated too close to the cricopharyngeus for intubation. In nine case series (total 154 patients) a success rate of 80–100% for relief of dysphagia has been reported. Injection therapy may also be used to control haemorrhage from bleeding tumours. Mediastinitis and tracheoesophageal fistula have been described in up to 2% of cases, particularly when larger doses of sclerosant are used. Postprocedure pain, oesophageal ulceration, and transient atrial fibrillation have also been reported. Recurrent dysphagia required the procedure to be repeated between 28 and 50 days. This recurrence rate, combined with the need for several initial sessions, results in the recommendation to reserve the use of injection therapy for tumours unsuitable for intubation.

Oesophageal intubation: Oesophageal intubation is an effective means of relieving dysphagia in a single procedure and is the chosen local procedure in the majority of cases. Rigid and semirigid plastic tubes (Atkinson, Celestin, Wilson-Cook) are less expensive than self expanding metal stents (Gianturco Z-stent, Wallstent, Ultraflex stent, Oesophacoil) though for the reasons outlined below the Wallstent and Ultraflex stent are the most commonly used prostheses locally. Four randomised trials have demonstrated some advantages with the narrow insertion apparatus and wider lumen of the metal stents. Two of these studies used the Gianturco Z-stent, one the Ultraflex stent, and the other used the Wallstent. A large multicentre NHS research and development study to examine this further is currently underway. Improvement in dysphagia in one procedure has been described in >90% of cases with both plastic tubes and metal stents. Only a small proportion of patients with plastic tubes are able to eat solids, with the remainder restricted to a liquid or semi solid diet. Between 50% and 80% of patients treated with a metal stent have been able to eat solids in some case series. However, three of four prospective randomised trials have shown no significant difference in dysphagia score following plastic or metal stent insertion. Overall complication rates of 10–15% for plastic tubes include oesophageal perforation (6–8%), haemorrhage (3– 5%), and aspiration pneumonia (2–16%). Procedural mortality of 2–12% has been demonstrated in different case series. Oesophageal perforation and life threatening haemorrhage occur in <1% and 4% of patients, respectively, following metal stent insertion. Procedural morbidity and mortality was significantly lower than with a plastic tube in three of four randomised controlled trials. In two of these studies general anaesthesia was used for plastic tube insertion, which may have influenced these results. Procedural complications with plastic and metal prostheses may be increased by prior radiation and/or chemotherapy. Three randomised trials and one retrospective study demonstrated shorter hospital stay following metal stent insertion, suggesting that the higher cost of these treatments
could be offset. Comparisons of metal and plastic tubes have not shown any differences in long term complication and re-intervention rates. Large case series have documented low

perforation rates following metal stent insertion of 0–2% but in addition to early re-intervention noted above, late morbidity occurred in approximately 25% of patients with both types. Late morbidity with self expanding metal stents is due to tumour ingrowth through the wire mesh of the stent, tumour overgrowth at the ends of the stent, stent migration, food bolus obstruction, haemorrhage, incomplete expansion, and persistent pain. One randomised trial, using a 22 mm covered Gianturco metal stent, demonstrated a small survival benefit of metal over plastic prostheses. This study also found that patients with a metal stent enjoyed their food more than those with a plastic tube, although no overall difference in quality of life was seen in this or other randomised trials of metal versus plastic tubes and plastic tube versus laser. There are no convincing data to support the use of palliative radiotherapy after insertion of oesophageal stents. It is not known whether metal stents alter the efficacy of radical radiotherapy and it would therefore seem sensible to delay insertion of a metal stent until after radical radiotherapy has been completed if this is envisaged. In cases where a stent is required prior to radical radiation, the use of a plastic stent may be preferable.

Tracheoesophageal fistulation: Several small case series have documented the effectiveness of Wilson-Cook cuffed prostheses and metal stents in the treatment of tracheoesophageal fistula and following oesophageal perforation during dilatation of a tumour. Complete sealing was documented in 87% of cases.

Oesophageal perforation: This occurs during tumour dilatation in approximately 2–5% of procedures. Both cuffed silicone (Wilson Cook) prostheses and covered metal stents have been used successfully in this situation with 100% success and no procedure related mortality.

Combination of radiotherapy and oesophageal intubation: Although there are no prospective studies combining stents with radiotherapy, there appears to be a role for stent placement in patients with recurrent dysphagia after radiotherapy, particularly in the presence of tight fibrotic strictures. This is usually a late event in the disease. Improved survival after stent insertion has either not been shown in those previously treated with chemotherapy or radiotherapy or is small and with the cost of extra morbidity and prolonged hospital stay. Several studies have found that previous chemotherapy or radiotherapy increases the risk of specific device related complications to the oesophagus by 3.5. Major complications included haemorrhage, oesophageal perforation, and broncho-oesophageal fistula formation.

Laser therapy

Laser therapy is appropriate for tumours with an exophytic component within the oesophageal lumen, however this treatment modality is not available locally. For lesions crossing the cardia, laser therapy is less successful in providing long term palliation of dysphagia than intubation although laser therapy prior to insertion of a stent may prevent stent failure. Approximately 50% of patients will be palliated by the initial laser treatment for the duration of their illness. Recanalisation for tumour regrowth can be successfully achieved with laser as many times as is needed and is more successfully achieved by laser than by dilatation or electrocoagulation. The complementary use of all modalities results in a better overall quality of swallow than intubation alone. Several studies have found that laser therapy produces better palliation initially reserving

intubation for salvage for those with a poor functional result to laser. Best results occur by individualising the palliative modality to the tumour characteristics and indeed different modalities may be appropriate at different stages in the patient's illness. Therefore, palliation is best performed in specialist units that have the full range of palliative modalities. Most studies show no difference in survival between patients treated with laser or prostheses although a trend to longer survival following laser is seen in some.

Combination of thermal (Nd: YAG) laser with radiotherapy: Randomised trials of intubation compared with laser therapy demonstrated a larger number of treatment sessions in those treated by laser. In a terminally ill group, an important aim is to maintain palliation with a minimum of interventions. Studies suggest a prolonged dysphagia free interval in those patients initially treated with laser who go on to receive external beam radiotherapy (30 Gy in 10 fractions). A single brachytherapy treatment (10 Gy) appears to prolong the dysphagia free interval even more. None of the trials with radiotherapy has shown a survival advantage using combination therapy although trends towards prolonged survival are seen in patients with locally advanced disease only (tumour stage T3N1M0). A small study published in abstract form only did however find a threefold increase in survival in these patients when treated with additional chemoradiotherapy following insertion of a self expanding metal stent. This area needs further investigation.

Thermal laser therapy for tumours of the cervical oesophagus: Tumours involving the cervical oesophagus account for less than 5% of all patients. Intubation is not safe within 2 cm of the upper oesophageal sphincter. Laser therapy or judicious and careful use of oesophageal dilatation is widely held to be the best form of treatment. Tracheo-oesophageal fistulation is more common for these types of tumour; patients must remain nil by mouth and receive nutrition via a gastrostomy.

Thermal laser for tumour overgrowth or ingrowth through stents: Tumour overgrowth at the ends of stents occurs in up to 10% of patients, particularly those treated with uncovered self expanding metal stents. Recanalisation can be achieved by laser therapy, diathermy, or stent replacement. Placing a second stent across the occluded area is effective although this results in further narrowing of the oesophageal lumen, which will result in a poorer quality final swallow. Nd: YAG laser has been used successfully in many patients in this situation, with stent patency restored after one or two treatment sessions. Care must be taken not to destroy the stent. As with other laser therapies, these can be done on a day case basis

PALLIATIVE TREATMENT: GASTRIC CANCER

Summary

- **Palliative chemotherapy for locally advanced and/or metastatic disease provides quality of life and survival benefit.**
- **Currently there is no indication to recommend second line chemotherapy. Its role should remain in the context of a clinical trial.**
- **Downstaging of locally advanced disease with chemotherapy is possible in individual cases, with anecdotal reports of prolonged survival following complete surgical resection. However, no randomised trials have been conducted to demonstrate a survival advantage from addition of surgery following palliative chemotherapy.**

Gastric and oesophagogastric junction cancer

First line palliative chemotherapy: Careful patient selection is important as those with good performance status and no comorbid disease are more likely to benefit from more aggressive treatment. There are now three randomised studies of chemotherapy compared with best supportive care that show a significant survival and quality of life benefit with chemotherapy. The preferred combination is epirubicin, cisplatin, and continuous infusion of 5-FU (ECF), which has a 65% response rate including 11% complete responses. In a randomised comparison of ECF with FAMTX, ECF was shown to have superior response (45% *v* 21%; p=0.0002) and survival (8.9 *v* 5.7 months; p=0.0009). Furthermore, ECF had a significantly greater two year survival (13.5% *v* 5.4%; p=0.03). Substitution of epirubicin by mitomycin C has shown similar response rates and survival, although ECF appears preferable on quality of life measures. Paclitaxel is currently being evaluated and combination with CF has a 51% response in advanced gastric cancer, with 10% complete responses.

Second line palliative chemotherapy: A number of phase I and II studies have demonstrated responses to new combinations following failure of first line chemotherapy. A combination of docetaxel and epirubicin for patients relapsing after 5-FU/cisplatin was reported as having a 21% response rate, 30% stable disease, and symptomatic improvement in 56%. Median survival was 5.7 months. Two phase II studies of irenotecan, which included previously treated patients, also indicated sensitivity in this setting.

Chemotherapy to downstage locally advanced disease for surgery: In a trial of ECF versus FAMTX, complete surgical resection was rendered possible in 10 of 43 patients with locally advanced disease treated with ECF; three had a pathological complete response. In a series of 30 patients with stage IIIA, IIIB, or IV gastric cancer treated with neoadjuvant etoposide, doxorubicin, and cisplatin, multivariate analysis showed that

complete clinical response to chemotherapy (n=8; p<0.01) and complete tumour resection (n=24; p<0.01) were the major independent predictors of long term survival.

FOLLOW UP

Follow up of patients with oesophageal and gastric cancer is controversial. The biology of both diseases is such that the majority are on active treatment with the minority attending for symptomatic review.

The aims are:

(1) To detect disorders of function either related to recurrent disease or benign complications of treatment.
(2) To assess and manage nutritional disorders.
(3) To provide psychosocial support for patients and their carers. This includes appropriate medical measures in liaison with palliative care.
(4) To facilitate audit of treatment outcome.

There is little consensus for the mode, duration, or intensity of follow up in patients with malignant disease. There is no evidence that intensive follow up improves the speed of detection of recurrent disease in oesophageal or gastric cancers. There is some concern that routine planned hospital appointments may contribute to delay in addressing problems as patients and general practitioners tend to ignore symptoms occurring between outpatient attendances.

The process of follow up should reflect the recommendations of the Calman-Hine report on the provision of services for those with cancer. All patients should be systematically followed up according to locally agreed protocols. Follow up could be by the hospital clinic or in primary care and the results of both methods should be subject to audit. Where follow up is by the hospital clinic it must be multidisciplinary to avoid the duplication of examinations and investigations with incumbent inconvenience to patients and carers. The first planned follow up examination should be by the multidisciplinary hospital team. Thereafter it could be either at the hospital clinic or in primary care. The patient should be consulted, and their wishes respected. A study of patients with various cancers found that the majority were in favour of regular follow up and thought that the advantages outweighed the disadvantages.

Patients who are being followed up either at the hospital clinic or in primary care should be able to seek help between review appointments if they are concerned, even if this occurs shortly after a review appointment. Follow up protocols need to meet the physical and psychological needs of the patient and carers as well as the early detection of recurrent disease. For individual general practitioners the additional workload is unlikely to be onerous and regularly planned contact should improve the doctor-patient relationship. Follow up by the general practitioner will not lead to fewer resources being needed at the hospital but could aid the hospital team in reducing waiting times and responding rapidly to requests for help. There needs to be rapid communication of information between hospital clinic and general practice and vice versa. The ability to

achieve this by fax or electronic means should be exploited. Clinical nurse specialists have a major role in providing continuity of care between primary and secondary care. Development of their role should include follow up to reduce the need for medically based review. This allows the facilitation of further hospital community or hospice review as required.

Nutritional support for patients is essential after both radical treatment and palliative management and there needs to be ready access for all patients to appropriate dietary advice.

MANAGEMENT OF RECURRENT DISEASE

Over seventy percent of patients with oesophago-gastric cancer, treated with curative intent, will develop recurrent disease. This will commonly present between follow up appointments in a variety of ways:

- general malaise and weight loss
- abdominal pain
- anaemia
- jaundice
- obstructive GI symptoms
- malignant ascites and effusions
- cutaneous or brain metastases

Local assessment:

- Initial assessment of symptoms and physical signs
- Routine blood count and biochemistry
- Nutritional assessment
- Counseling and support
- Discussion at local MDT meeting

If there is clear clinical evidence of disease recurrence but the patient is too frail for or chooses to have no further treatment, it may be appropriate to refer to the palliative medicine team for symptom control and best supportive care at this stage.
Patients fit enough for and seeking further therapy, or unfit but wishing to have staging for prognostic purposes, will be offered any of the following investigations:

- Staging CT chest/abdomen/pelvis
- US scan of liver
- Gastroscopy
- Bone scan
- CT brain
- Biopsy skin nodules and accessible nodes

All patients with recurrent disease will then be referred in to the Specialist MDT.
Records on the SCR are updated for outcome audit purposes.

Review by Specialist MDT:

Additional investigations may be required for confirmation of recurrence and characterization of equivocal lesions:

- PET-CT
- EUS guided FNA
- EBUS guided FNA
- percutaneous biopsy
- HER2 receptor testing of stored tissue
- laparoscopy

Review of the results of these investigations by the Specialist MDT will help guide decisions on palliative treatment.

Palliative chemotherapy:

Various regimens are available and will be offered in the local hospital units wherever possible.
EOX will be supplemented with Herceptin for recurrent gastric cancer and gastro-oesophageal adenocarcinoma with a high expression of HER2 receptors.
Docetaxel is offered in the COUGAR-02 trial.
Other second line therapies may require tertiary referral to the Christie Hospital.

Radiotherapy:

Patients with recurrence of SCC in the mid/upper mediastinum and neck may be selected for palliative radiotherapy and will be assessed at the Rosemere Centre in Preston. Radiotherapy is also available for the management of painful bony metastases and the control of brain metastases.

Stent placement:

For luminal recurrences and relief of obstruction by extrinsic compression, stent placement may be requires. Oesophageal stents can be placed by members of the local GI teams. Gastric and duodenal stent placements are offered by the specialist team radiologist. Bronchial stenting is available at Preston.

Endoscopic therapies:

In some instances, simple dilatations may be appropriate, and the use of Argon Plasma Coagulation can be helpful in controlling exophytic and bleeding lesions. This therapy is available on all local sites.

Nutritional support:

Input from the nutritional team will help plan the method to be used:

- oral dietary supplements
- fine bore naso-gastric feeding

- Jejunostomy placement (preferably radiological – RIG)

Surgery:

Rarely is surgery appropriate for esophagogastric cancer recurrence but resection is considered for recurrent gastric cancer in the gastric remnant following partial and subtotal gastrectomy. Other indications include solitary peripheral lymph-nodes and skin lesions, solitary liver metastases which remain stable with chemotherapy and solitary brain metastases. Patients with single site intestinal obstruction from peritoneal recurrence can benefit from a surgical by-pass procedure.

Symptom control:

Control of chronic pain, nausea and vomiting is addressed by the local oncology team in conjunction with the palliative medicine team covering primary and secondary care. Sometimes interventions by the pain clinic team will be sought.

Psychological support:

A holistic approach to the patients needs will ensure that psychological support is available, and the patient is made aware of the community-based support groups in the different localities. Plans for end-of-life care are discussed with the patient.

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APPENDIX I

Referral guidelines for upper gastrointestinal cancers

• Dysphagia

• Dyspepsia combined with one or more of these alarm symptoms:
Weight loss
Anaemia
Anorexia

• Dyspepsia in a patient aged 55 years or more with at least one of the following "high risk" features:
Onset of dyspepsia less than
one year ago
Continuous symptoms since onset

• Dyspepsia combined with at least one of the following known risk factors:
Family history of upper gastrointestinal cancer in more than one first degree relative
Barrett's oesophagus
Pernicious anaemia
Peptic ulcer surgery over 20 years ago
Known dysplasia
Atrophic gastritis
Intestinal metaplasia

• Jaundice

• Upper abdominal mass

APPENDIX II

TNM classification of oesophageal and gastric cancers

Classification	Oesophagus	Gastric
T1	Lamina propria, submucosa	Lamina propria, submucosa
T2	Muscularis propria	Muscularis propria, subserosa
T3	Adventitia	Penetrates serosa
T4	Adjacent structures	Adjacent structures
N1	Regional nodes	1-6 nodes
N2		7-15 nodes
N3		>15 nodes
M1	Distant metastasis	Distant metastasis

NB: Additional M staging for oesophageal tumours as follows:

Tumours of the lower oesophagus:

M1a coeliac nodes
M1b other distant metastasis

Tumours of the mid thoracic oesophagus:

M1b Distant metastasis including non-regional lymph nodes

Tumours of the upper thoracic oesophagus:

M1a Cervical nodes
M1b Other distant metastasis

NOTES ON RECORDING DATA ITEMS:

a) OESOPHAGEAL CANCER

GROSS DESCRIPTION

Specimen measurements

The length of the oesophagus can be difficult to determine due to its tendency to contract. It loses ¼ of its length immediately upon removal and can be as little as 1/3 of its natural length if fixed without being pinned out. This should thus be specified.

Tumour measurements

Most resection specimens will consist of an oesophago-gastrectomy specimen. It is sometimes difficult to decide whether a lesion should be classified as a high gastric carcinoma with oesophageal invasion, a cardiac tumour which is straddling the gastro-oesophageal junction, or a low oesophageal carcinoma invading the stomach. For the purposes of this data set, a lesion is said to be an oesophageal carcinoma when more than half (measure on the mucosal aspect) is above the gastro-oesophageal junction (GOJ). The GOJ is often obvious on the mucosal surface. Sometimes, however, large tumours obliterate the junction. Alternatively, extensive Barrett's oesophagus can make it difficult to identify the GOJ. In these situations, the junction is probably most easily identified by the highest extent of the peritoneal reflection on the serosal surface. The size and position of the tumour will allow its location with respect to the GOJ to be determined.
The macroscopic appearance of the tumour has little contribution to the prognosis, with the exception of polypoid tumours.

MICROSCOPIC FEATURES

Histological type of tumour

The vast majority of these lesions will be adenocarcinomas and squamous carcinomas, with a few adenosquamous lesions and small cell carcinomas. Whilst the type of carcinoma may have little influence on prognosis in the majority of lesions[7], in very early cancers (T1) it may be better to have an adenocarcinoma – they have less local recurrence and fewer new primary lesions. Irrespective of the prognostic implications it provides useful validation of the presurgical diagnosis which may be important in adjuvant therapy decisions.

Tumour differentiation

Opinion is divided upon the prognostic significance of tumour differentiation. In some studies, it was prognostically significant for squamous carcinomas[9], adenocarcinomas or both. However, in one large study [it] was not significant. Thus, as it is usually easy to assess and may be important prognostically, it is included in the minimum data set.

Depth of invasion

Occasionally an oesophageal resection will be performed upon a patient who has had multiple biopsies showing high grade dysplasia, usually in the context of Barrett's oesophagus. These patients almost always have invasive adenocarcinoma in the resection specimen, but occasionally a resection will show only high grade dysplasia. The depth of invasion is assessed according to the TNM staging system and is one of the most consistent predictors of prognosis. It is often the only independent prognostic indicator

on multivariate analysis. Some authors have attempted to go further and distinguish mucosal and submucosal invasion, although there is little support for this.

Serosal involvement

Many distal oesophageal carcinomas will involve the proximal stomach. At this site there is no circumferential margin, but there is a serosal surface. Whilst there is no evidence to confirm or refute serosal involvement as an important prognostic indicator in oesophageal carcinoma, it is undoubtedly so in the stomach and for this reason is included in the minimum data set.

Proximal and distal margins

The proximal (upper) and distal (lower) resection margins of the oesophagus require histological exclusion of involvement. There is good evidence that involved proximal margins increase the likelihood of recurrence but less evidence for distal margins. The proximal margin of the oesophagus should always be sampled, no matter what the distance from the tumour because of the risk of discontinuous foci of carcinoma in the proximal oesophagus.

Circumferential margin

Examination of the circumferential resection margin (CRM) is rather more contentious. In some sites, such as the cervix in radical surgery, the value of detection of CRM involvement is unquestioned. In the rectum it is accepted for its crucial role in determining which patients go on to have local adjuvant treatment. However, before Sagar et al published their study of CRM involvement in the oesophagus, few studies even mentioned this as a possible parameter. CRM involvement was found to be a strong predictor of poor 2 year survival. CRM involvement probably provides a good indication of the degree of tumour spread and the extent of resection and provides useful information in comparing different surgical techniques.

This is supported by the fact that, whilst gastric cardiac tumours have on the whole a worse prognosis than other gastric tumours, it is only in stage T2 tumours (ie penetration of muscle coat but not serosal involvement) that this effect is seen.

In the absence of negative evidence, it is included in the minimum data set and the presence of carcinoma less that 1mm from a circumferential margin is considered to be the criterion for margin involvement.

Vascular invasion

Vascular invasion is an effective prognostic indicator. Different studies have detected involvement in different ways, some using special stains and some specifying venous over lymphatic invasion. Many showed a significant effect on univariate analysis and in one large study it was as independently prognostic as depth of invasion on multivariate analysis. There is no separate data comparing intra and extramural vascular invasion.

Perineural invasion

There is less evidence for perineural invasion as a prognostic indicator[10] and the only significance here was lost on multivariate analysis.

Lymph node stage and numbers of involved nodes

All studies in which crude lymph node status is assessed show it to be a significant indicator of prognosis and in many of those papers it was the most significant prognostic indicator. The TNM staging system indicates only whether or not lymph nodes are involved, with no subclassification into N2 or N3, unlike the system used in the stomach.

However, when assessed, large numbers of involved nodes is usually, although not always a significant factor. It also provides information about the extent of the resection and so is included in this minimum data set.
There is little information upon the significance of the location of involved lymph nodes, or on features such as extracapsular invasion. In the absence of such evidence, these features are not included in the data set.
The search for involved lymph nodes has been refined in some sites by the use of immunohistochemistry and serial sections to detect micrometastases. Only one study has identified micrometastases in the lymph nodes around the oesophagus[20] using Ber-EP4. These authors found that immunohistochemical detection of malignant cells in lymph nodes worsened prognosis of patients who were conventionally node negative. This observation needs, however, to be confirmed in further studies before its clinical relevance can clearly be established. Until then it is not recommended that immunohistochemistry is adopted in routine practice.

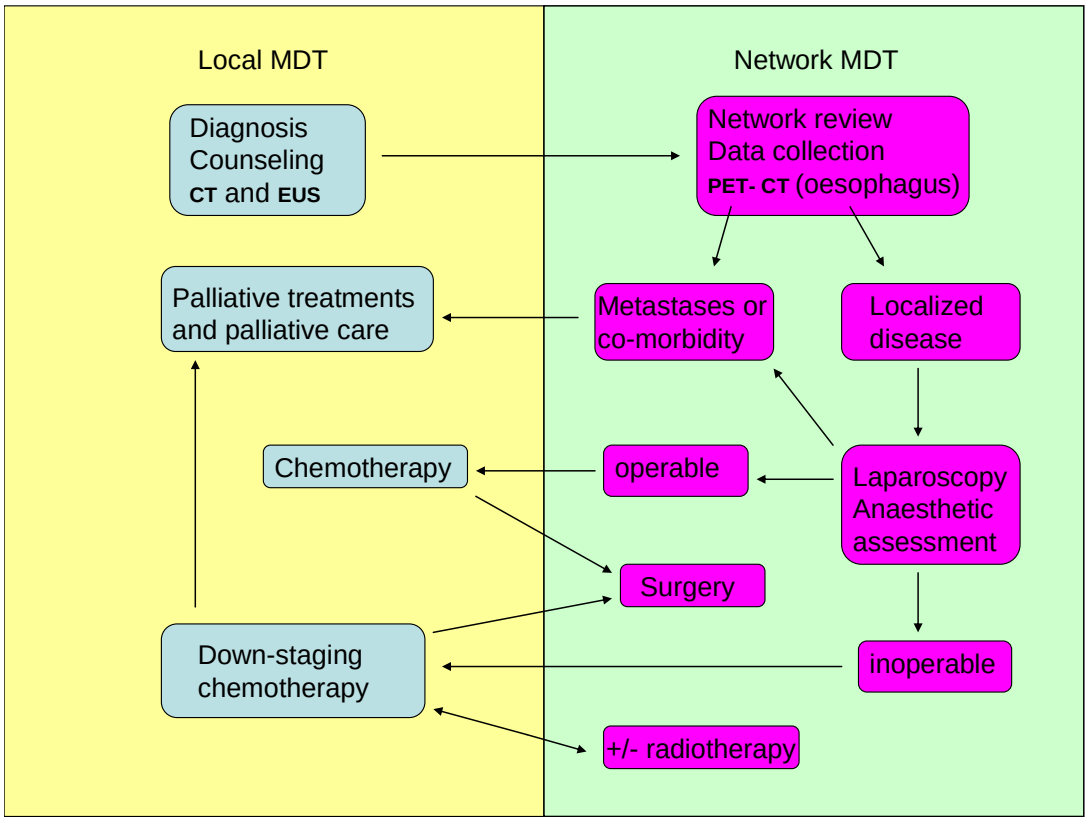
Barrett's metaplasia
Some studies indicate a positive prognostic effect of the presence of Barrett's metaplasia in the adjacent oesophagus. Whilst this may identify less advanced tumours many of these patients may have been screened for Barrett's and documentation of its presence is useful for audit.

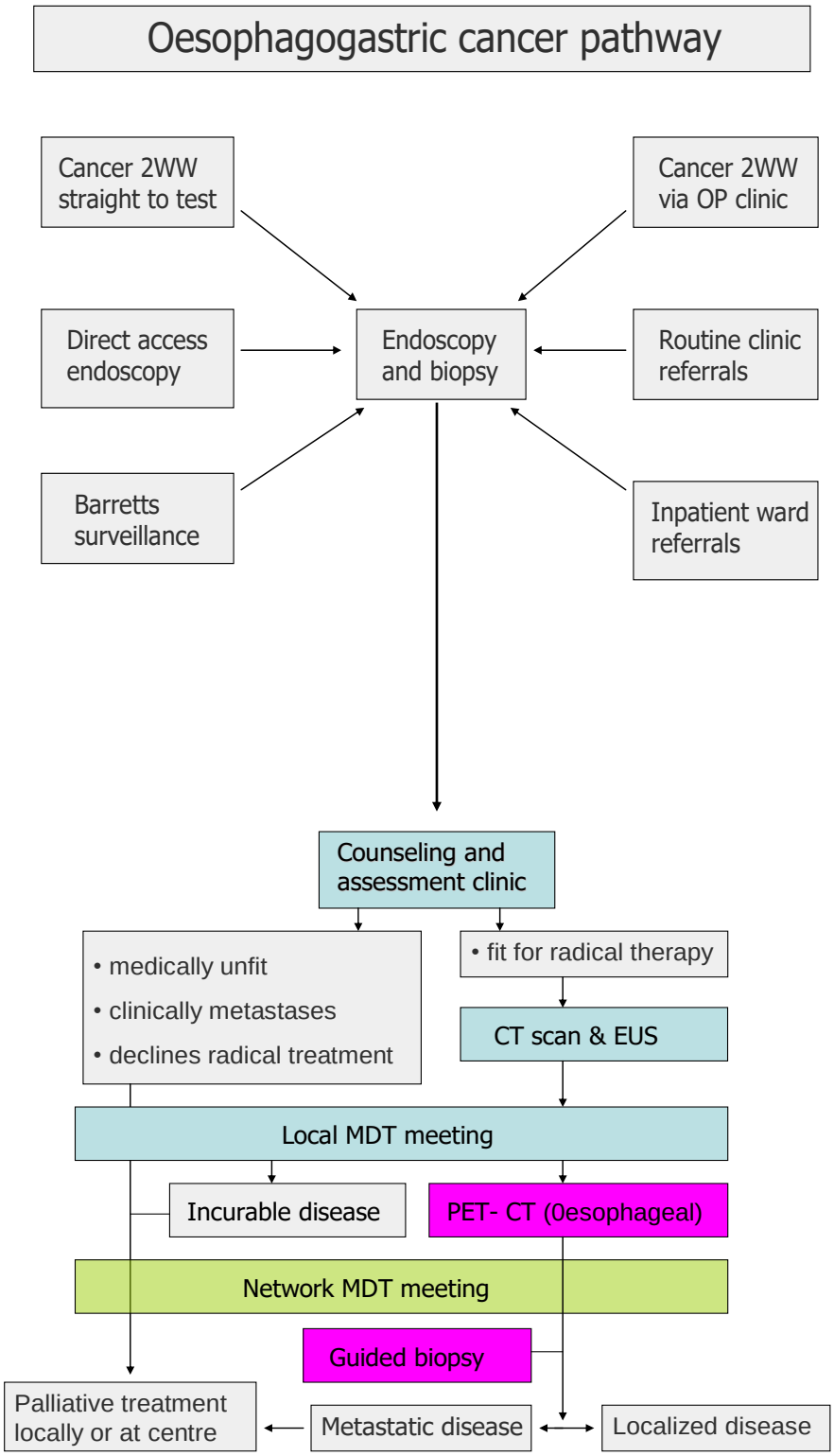
Other markers
Many other markers of prognosis have been investigated, including ploidy, angiogenesis, CD44 and EGFR. Many show some prognostic significance but without confirmatory evidence in larger studies the use of such special techniques is not justified in a minimum data set.

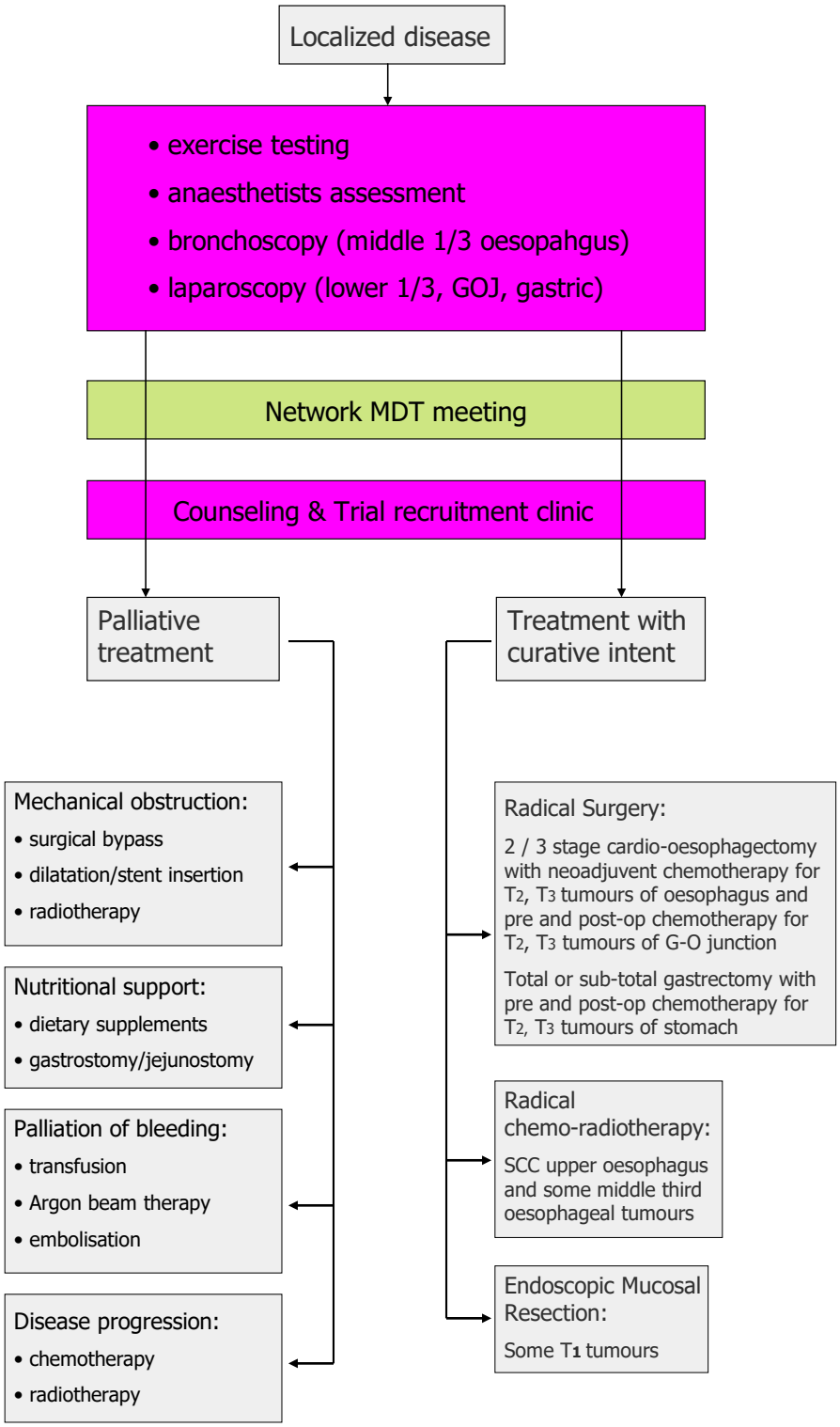
Minimum data set for an initial biopsy diagnosis of oesophageal carcinoma
An initial biopsy report should identify the type of carcinoma – squamous cell or adenocarcinoma. The presence of overlying squamous cell dysplasia, glandular dysplasia or Barrett's metaplasia will also provide support for a primary oesophageal origin and so should also be included if present. The depth of invasion may also be useful information. Submucosal invasion (as opposed to intra-mucosal invasion only) is a prognostic indicator of nodal metastases. This would be of little use in a resection specimen where the nodes are available for dissection and thus the TNM classification of depth of invasion (which does not differentiate between mucosal and submucosal invasion) is used for resection specimens. However, it may be helpful for the clinicians to know if submucosal invasion is identifiable in a biopsy specimen and thus should be included in biopsy reports.

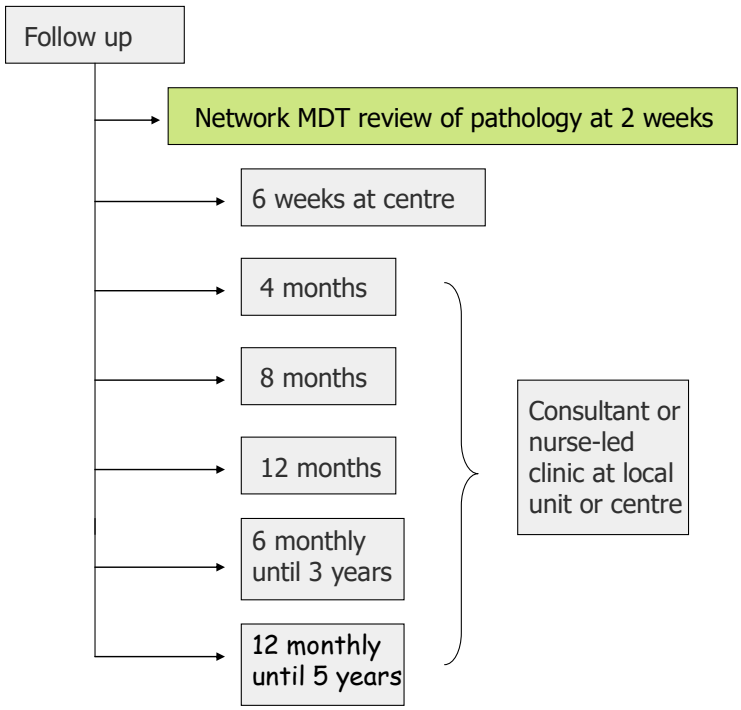
APPENDIX III

Clinical pathway of care:
Roles of the local and the network MDTs




Oesophagogastric cancer pathway
Cancer 2WW straight to test
Cancer 2WW via OP clinic
Direct access endoscopy
Endoscopy and biopsy
Routine clinic referrals
Barretts surveillance
Inpatient ward referrals
Counseling and assessment clinic
• medically unfit
• clinically metastases
• declines radical treatment
• fit for radical therapy
CT scan & EUS
Local MDT meeting
Incurable disease
PET- CT (0esophageal)
Network MDT meeting
Guided biopsy
Palliative treatment locally or at centre
Metastatic disease
Localized disease


Localized disease
• exercise testing
• anaesthetists assessment
• bronchoscopy (middle 1/3 oesopahgus)
• laparoscopy (lower 1/3, GOJ, gastric)
Network MDT meeting
Counseling & Trial recruitment clinic
Palliative treatment
Treatment with curative intent
Mechanical obstruction:
• surgical bypass
• dilatation/stent insertion
• radiotherapy
Nutritional support:
• dietary supplements
• gastrostomy/jejunostomy
Palliation of bleeding:
• transfusion
• Argon beam therapy
• embolisation
Disease progression:
• chemotherapy
• radiotherapy
Radical Surgery:
2 / 3 stage cardio-oesophagectomy with neoadjuvent chemotherapy for T2, T3 tumours of oesophagus and pre and post-op chemotherapy for T2, T3 tumours of G-O junction
Total or sub-total gastrectomy with pre and post-op chemotherapy for T2, T3 tumours of stomach
Radical chemo-radiotherapy:
SCC upper oesophagus and some middle third oesophageal tumours
Endoscopic Mucosal Resection:
Some T1 tumours


Follow up
Network MDT review of pathology at 2 weeks
6 weeks at centre
4 months
8 months
12 months
6 monthly until 3 years
12 monthly until 5 years
Consultant or nurse-led clinic at local unit or centre

APPENDIX IV

Network Patient Information Leaflets

- Diagnosis Information
- Investigations for Oesophageal/Stomach Cancers
- Oesophageal and Gastric/ Duodenal Stent
- Partial & Total Gastrectomy and Oesophagectomy
- Jaundice
- Liver Resection
- Whipples Resection
- Information for patients on MDT meetings
- Upper GI Nurse Specialist services

http://www.cancerlancashire.org.uk/index.php?option=com_content&view=article&id=225%3Apatient-information-leaflets-upper-gi&catid=901&Itemid=182

Appendix V

Prague Criteria for endoscopic assessment of Barrett's Oesophagus

Please follow the link below to download criteria in a step by step guide:

http://iwgco.com/e107_plugins/content/content.php?content.5

Appendix VI

BARRETT'S OESOPHAGUS RADIOFREQUENCY ABLATION

Pre-procedure preparation

Remain on Aspirin/Clopidogrel
Withdraw anticoagulation
Potent PPI for >1 week

Procedure

GA initially/poor intolerance to endoscopy, or sedation and analgesia.
Procedure time 45-60 mins.
OGD
- Detailed assessment
- Mucolytic: N-acetyl cysteine 1% with water (NOT N/saline)
- Visible lesions: biopsy/ER, reschedule in 3 months
- Stricture: dilate to 18 mm balloon, reschedule in 3 months
- Locate GOJ, S-C junction

Sizing
- Commence 5 cm above S-C junction
- 1 cm intervals
- Terminate at GOJ
- Blood on balloon: reschedule in 3 months

First ablation HALO 360
- 2 sizes below recommended sizing balloon diameter
- Under direct endoscopic vision 1 cm above S-C junction
- Inflate and aspirate
- Ablate

Clean
- Mucolytic
- Cleaning cap (Olympus soft cap)

Second ablation HALO 360
Residual ablation HALO 90
- Indications: residual patches/tongues, OGJ, strictured areas

Post-procedure

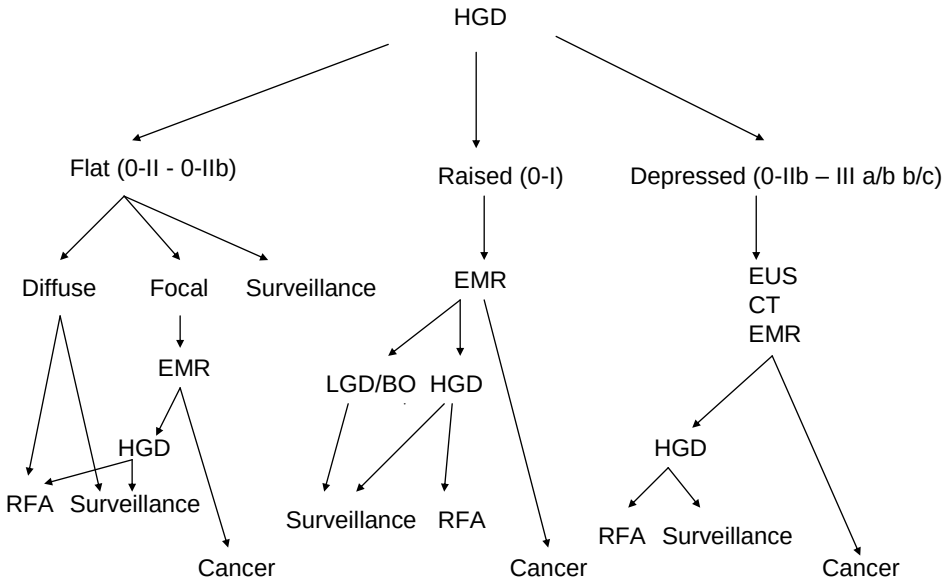
Side effects: generally minor and resolve by day 4.
- Pain
- Odynophagia
- Dysphagia
- Fever

Rare side effects: more likely in previous strictures, ulceration, endoscopic therapy, surgery.
- Mucosal laceration
- Stricture
- Perforation
- Haemorrhage
- Stricture

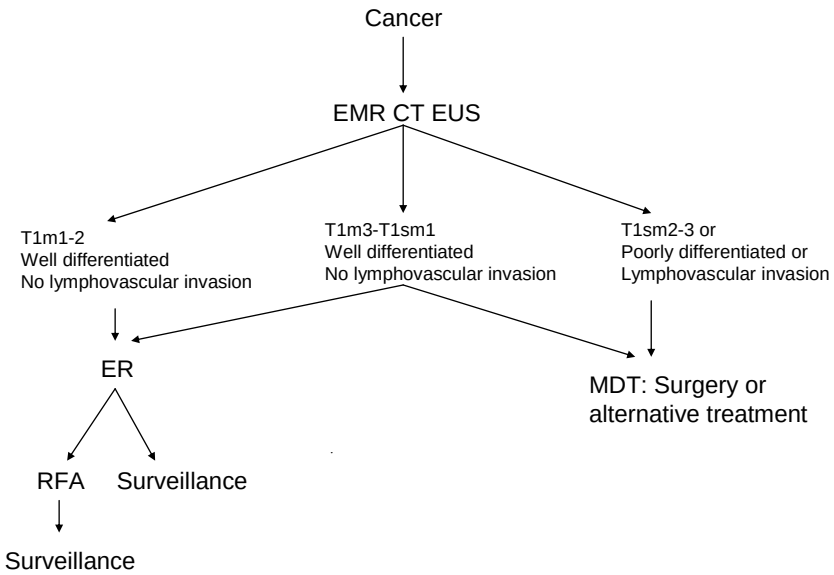
Acid suppression e.g. Esomeprazole 40 mg BD for 1 month
Liquid diet for 1 day, soft diet for 1 week
No NSAIDs for at least 1 week.

APPENDIX VII

HGD

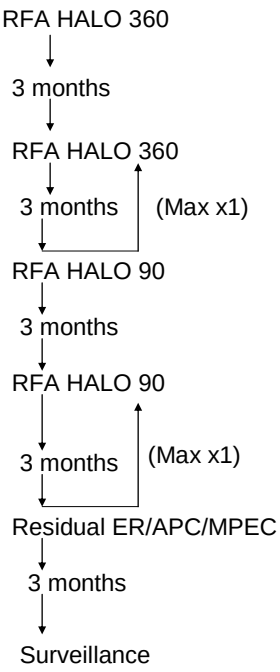


Cancer



APPENDIX VII

RFA



Surveillance following RFA, EMR