



Management of oesophageal and gastric cancer

A national clinical guideline

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June 2006

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1⁺⁺ and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group

Scottish Intercollegiate Guidelines Network

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A national clinical guideline

This guideline is dedicated to the memory of
Gwen Harrison and Phoebe Isard.



June 2006

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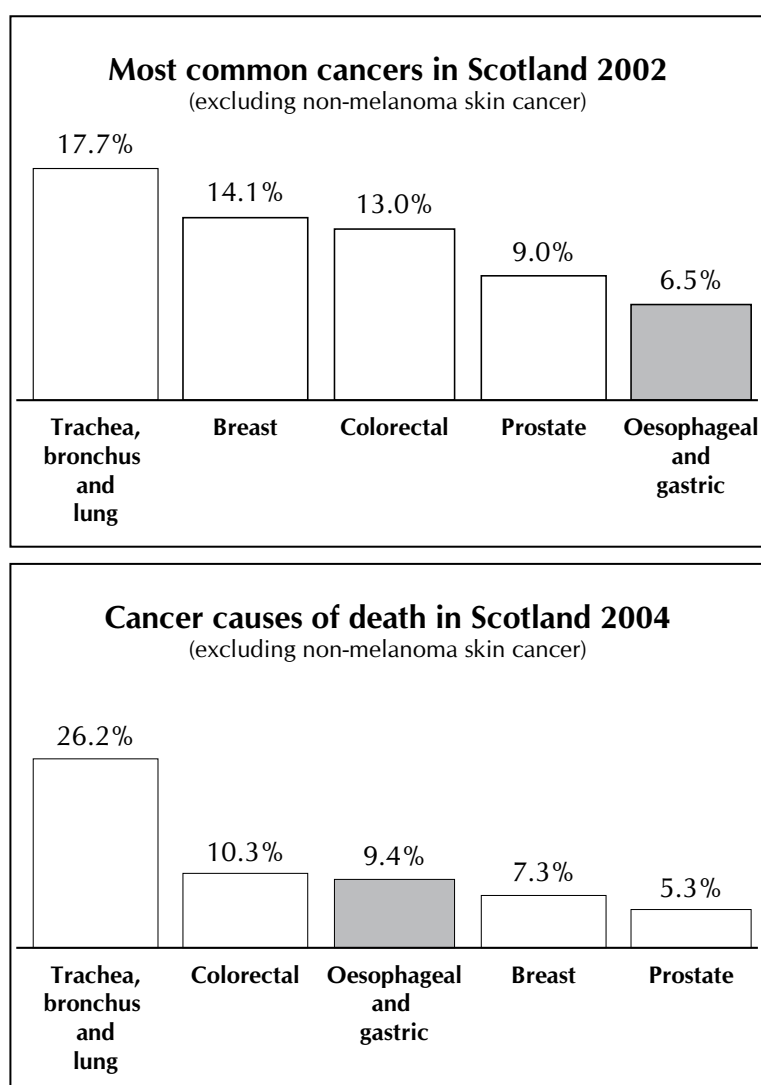
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1 Introduction

1.1 BACKGROUND

Approximately 1,700 patients are diagnosed with oesophageal or gastric cancer in Scotland each year. Taken together (and excluding non-melanoma skin cancer), they constitute the fifth most common cancer in Scotland, accounting for 6.5% of all newly diagnosed cancers. Due to the poor prognosis of patients with these cancers they are the third most common cause of cancer death in Scotland and account for 9.4% of all cancer deaths (see Figure 1).

Figure 1 Cancer diagnoses and cancer deaths in Scotland¹



The median age of patients at presentation is 72 years, with these cancers rarely being diagnosed in people aged less than 40 years.² They are more common in men (male: female ratio = 2:1 approximately) and there is a significant association between deprivation and both incidence and mortality.³

Patients presenting with symptoms of oesophageal and gastric cancer almost invariably have advanced disease. The median observed survival from diagnosis is 8.4 months and around 40% of patients are alive at one year.⁴ Although five-year survival has doubled in the period 1977 to 2001 for patients with oesophageal cancer (males: 4% to 10%; females: 7% to 13%) and gastric cancer (males: 6% to 13%; females: 9% to 18%) it remains low.

1.2 SCOTTISH AUDIT OF GASTRIC AND OESOPHAGEAL CANCER

The Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) completed a prospective audit of the treatment of 3,293 oesophageal and gastric cancer patients in Scotland diagnosed over the period July 1997 – July 1999, with a minimum of one-year follow up on each patient. Forty five per cent of the observed cancers were oesophageal, 39% gastric and 16% were located at the oesophagogastric junction. Adenocarcinoma of the oesophagus was more frequent than squamous cancer, the ratio being 5:4.²

The audit is a complete dataset that provides important epidemiological background to the guideline and descriptive material on Scottish practice. It has been referenced throughout the guideline where appropriate. The audit is published in full at www.show.scot.nhs.uk/crag/committees/CEPS/reports/SAGOC_reoort_Contents.htm

1.3 THE NEED FOR A GUIDELINE

The need for the development of an evidence based guideline was highlighted as a recommendation of the SAGOC audit. The audit reported high postoperative mortality rates (30 day: 12.9%) and revealed low postoperative survival (one year: 53%; two year: 32%). The audit also demonstrated wide regional variations in the investigation and management of patients.

There is a need to improve outcomes for patients with potentially curable oesophageal and gastric cancer as well as a need to improve services for the majority of patients who die as a result of their cancer. As the average life expectancy of patients is short, coordinated service provision between hospital, community and palliative care services is essential. The SAGOC audit revealed large differences throughout Scotland in the access to, and use of, palliative techniques.

1.4 REMIT OF THE GUIDELINE

This guideline provides recommendations based on current evidence for best practice in the management of patients diagnosed with oesophageal or gastric cancer. The guideline adopts a multidisciplinary approach with involvement of all professionals in the care of patients. Included are all patients with squamous cancer of the thoracic oesophagus and all patients with adenocarcinoma of the oesophagus or stomach. The guideline remit excludes squamous cancer of the cervical oesophagus, which is covered in the SIGN guideline on head and neck cancer,⁵ as well as other rare tumours including lymphoma, small cell cancer and gastrointestinal stromal tumours.

This guideline does not include detailed guidance for the provision of diagnostic endoscopy services.

The management of the pre-malignant condition Barrett's oesophagus is also beyond the remit of this guideline with the exception of patients with high grade dysplasia (HGD). Guidelines for the diagnosis and management of Barrett's oesophagus are published by the British Society of Gastroenterology.⁶

The aims of this guideline are:

- to improve care and outcomes for patients with oesophageal and gastric cancer
- to provide guidance in patient management in order to reduce the wide variations in current practice observed throughout Scotland
- to encourage appropriate referral and early diagnosis in the general population and in high risk groups
- to optimise care delivery for oesophageal and gastric cancer patients at all stages of their disease by informing local protocols for implementation by managed clinical networks
- to ensure that all patients with oesophageal or gastric cancer are offered the best chance of cure or palliation irrespective of where they present or are treated.

1.5 TARGET USERS OF THE GUIDELINE

The patient journey from presentation to the general practitioner (GP), referral for investigation, through to diagnosis and specialist referral is a multistep process.

The effective management of patients with oesophageal and gastric cancer requires a multidisciplinary approach. The investigation and management of each new patient requires access to a multidisciplinary team consisting of surgeons, gastroenterologists, endoscopists, oncologists, nurses, dietitians, radiologists, pathologists, and anaesthetists. Through this multidisciplinary team the patient should closely interact with a wider team of palliative care specialists and general practitioners. Patients should have access to patient support groups and adequate information. This guideline will be of interest to all of these professionals, patients and their carers as well as to managers and policy makers.

1.6 DEFINITIONS

The term “oesophagogastric junction tumour” covers lower oesophageal adenocarcinoma, junctional tumours and cancer of the cardia.

The Siewert classification is used to subdivide oesophagogastric junction tumours into type I, II, and III.⁷ The classification covers the area 5 cm either side of the gastro-oesophageal junction.

Type I - the centre of the cancer or more than two thirds of identifiable tumour mass is located > 1 cm proximal to the anatomical gastro-oesophageal junction

Type II - the centre of the cancer or the tumour mass is located in an area extending 1cm proximal to the gastro-oesophageal junction to 2 cm distal to it

Type III - the centre of the tumour or more than two thirds of identifiable tumour mass is located >2 cm below the gastro-oesophageal junction.

Barrett’s oesophagus is identified as an oesophagus in which the normal squamous lower oesophageal epithelium has been replaced by a metaplastic columnar epithelium which is visible macroscopically.

1.7 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.

1.8 REVIEW AND UPDATING

This guideline was issued in 2006 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk.

2 Risk factors and risk factor modification

2.1 RISK FACTORS

The examination of risk factors must consider each cancer site individually (oesophageal, gastric and oesophagogastric junction), and distinguish squamous cancer and adenocarcinoma of the oesophagus.

2.1.1 AGE AND SEX

Oesophageal and gastric cancers occur mainly in people over 55 years of age. The overall median age at presentation is 72. Both cancers have a peak incidence at an older age in women than in men. Male sex is a risk factor for squamous cancer of the oesophagus (male:female 2.3:1) and for oesophagogastric junction cancer (male:female 1.9:1).²

2⁺⁺

2.1.2 DEPRIVATION

Deprivation is a risk factor for development of squamous cancer of the oesophagus and for gastric cancer.² There is no discernible relationship between deprivation and tumour incidence for adenocarcinoma of the oesophagus or for cancer at the oesophagogastric junction.

2⁺⁺

2.1.3 TOBACCO

Tobacco smoking increases the risk of squamous cancer of the oesophagus approximately nine fold compared with age and sex matched controls. It also increases the risks for oesophagogastric junction cancer and gastric cancer, though to a lesser extent. It is not clear whether smoking is a risk factor for oesophageal adenocarcinoma.^{8,9}

2⁺⁺

2.1.4 ALCOHOL

Squamous cancer of the oesophagus and gastric cancer are associated with alcohol consumption. Alcohol consumption does not appear to be a risk factor for adenocarcinoma of the oesophagus or for cancer at the oesophagogastric junction.⁸⁻¹⁰

1⁺

2.1.5 BODY MASS INDEX

Increasing body mass index (BMI) is associated with an enhanced risk of oesophageal adenocarcinoma and with a risk of oesophagogastric junction cancer.^{11,12} There is no association of high BMI with gastric cancer or with squamous cancer of the oesophagus.

2⁺⁺

2.1.6 DIET

The relationships between dietary components and the risks of gastric and oesophageal cancer are complex. In general, diets with substantial intakes of plant-based foods are associated with lower risk and those with high intakes of animal-based foods with higher risk.¹³ Increased dietary fibre intake is associated with reduced risk, especially in respect of cancer at the oesophagogastric junction.¹⁴ Diets with high intakes of antioxidants such as vitamin C, vitamin E and beta carotene are associated with reduced risk of oesophageal and gastric cancers.¹⁵⁻¹⁷ In the USA, below average consumption of fruit and vegetables is a demonstrable risk factor for oesophageal but not for gastric cancer⁹ whereas a diet low in fruit and vegetables was a risk factor for gastric cancer in a Brazilian case control study.¹⁸

2⁺⁺

B A healthy lifestyle (*not smoking, not consuming excess alcohol, avoiding obesity and maintaining a good dietary intake of fibre, fruit and vegetables*) is associated with reduced risk of oesophageal and gastric cancer and should be encouraged.

2.1.7 INHERITANCE

Gastric cancer shows familial clustering, indicating that family history is a risk factor. Environmental factors shared by family members may explain much of this clustering effect in gastric cancer and may also contribute to the familial risk of oesophageal cancers. Inheritance almost certainly has a role in the risk of developing both squamous and adenocarcinoma of the oesophagus. Familial gastric cancer, for example due to E-cadherin gene mutation, is also recognised but overall, heredity makes only a very small contribution to the occurrence of gastric and oesophageal cancer.¹⁹⁻²²

3

2.1.8 PREDISPOSING CONDITIONS

Inherited conditions, previous surgery, achalasia, coeliac disease and pernicious anaemia

The squamous oesophageal cancer risk in rare inherited conditions such as tylosis is well recognised.²³ Previous peptic ulcer and previous gastric surgery both predispose the development of gastric cancer.^{24,25} Pernicious anaemia is also known to predispose patients to gastric cancer and to squamous oesophageal cancer.²⁶ Achalasia and coeliac disease present a small increased risk of squamous cancer of the oesophagus.^{27,28}

3

Case series studies in patients with pernicious anaemia or previous gastric surgery generally do not support the use of endoscopic surveillance to try to identify early cancers.^{24,25,29-31} Surveillance has not been appraised in a randomised controlled trial.

3

Gastro-oesophageal reflux and Barrett's oesophagus

Longstanding symptomatic gastro-oesophageal reflux disease (heartburn) is a recognised risk factor for Barrett's oesophagus and oesophageal adenocarcinoma.³² In the UK, patients with Barrett's oesophagus have a 1% per annum risk of developing oesophageal adenocarcinoma.³³ The risk of cancer is two or three times greater in patients with Barrett's oesophagus than in patients with longstanding heartburn in the absence of Barrett's.³⁴ In Scotland, only 14% of oesophageal adenocarcinomas occur in patients previously known to have Barrett's oesophagus.² A systematic review reported a preoperative prevalence of Barrett's oesophagus of 5% in patients with oesophageal adenocarcinoma.³⁵ There may also be an association between gastro-oesophageal reflux and cancer at the oesophagogastric junction.^{32,36}

1+
2+

There are no randomised controlled trials to test the hypothesis that surveillance of patients with Barrett's oesophagus prevents cancer or improves survival.^{37,38} The British Society of Gastroenterology guidelines currently recommend that the decision to embark on surveillance endoscopy should be taken on an individual patient basis and that where surveillance is undertaken this should be carried out at two year intervals.⁶

2++
4

The patients with Barrett's oesophagus who are at highest risk of malignant progression are: men, patients over 60, and those with any of the following on index endoscopy: ulceration and severe oesophagitis, nodularity, stricture, or dysplasia.³⁸⁻⁴⁰

2+

Despite inconsistency in the surveillance protocols used, there is general agreement from case series and retrospective analyses that surveillance detected cancers are associated with significantly better outcomes than those detected in symptomatic patients.⁴¹⁻⁴⁵ The interpretation that may be put on these findings is limited by lead time bias and length bias such that the findings cannot be interpreted as showing survival advantage for those under surveillance.⁴⁶

2-
32.1.9 *HELICOBACTER PYLORI*

The presence of *Helicobacter pylori* infection is associated with a two to threefold increase in the risk of developing gastric cancer.⁴⁷⁻⁵⁰ *Helicobacter pylori* infection is associated with both diffuse and intestinal types of gastric cancer,^{47,51} though the strength of association is greater for the intestinal type.⁴⁸ In Western populations, gastric cancer is mainly associated with infection by cagA strains of the organism.⁵¹ The relationship between *Helicobacter pylori* infection and cancer of the oesophagogastric junction is still unclear. Although one meta-analysis has concluded that there is no association between them,⁴⁷ two other meta-analyses consider the available data so limited that no conclusion can be made.^{48,49}

2+

There is a reduced risk of oesophageal adenocarcinoma among individuals with *Helicobacter pylori* infection in the stomach, suggesting that in this instance infection may have a protective effect in respect of this cancer.⁵² 2+

2.2 RISK FACTOR MODIFICATION

Studies directly examining the benefits of risk factor modification are few resulting in a lack of robust evidence on which to base clinical advice.

Stopping smoking reduces the risk of subsequent development of gastric cancer and of squamous oesophageal cancer.^{9,53} The impact of weight reduction, reduced alcohol intake and increased dietary fruit and vegetable consumption on gastric and oesophageal cancer risk remains to be established. 2+

The evidence suggests that medical or surgical treatment of gastro-oesophageal reflux does not prevent subsequent development of oesophageal adenocarcinoma.⁵⁴⁻⁵⁸ 2+

C Reduction of risk of progression to adenocarcinoma is not an indication for anti-reflux surgery in patients with Barrett’s oesophagus.

Although *Helicobacter pylori* eradication would appear to offer a means of reducing gastric cancer risk, it did not reduce the frequency of gastric cancer development in one study conducted in a Chinese population with a very high gastric cancer incidence. The incidence was reduced in those patients who had no intestinal metaplasia, gastric atrophy or dysplasia on entry to the study.⁵⁹ The relevance of these results to European populations is uncertain. 2++

It is possible that *Helicobacter pylori* eradication may increase the risk of oesophageal adenocarcinoma. Further studies of the benefits and harms of *Helicobacter pylori* eradication are awaited.

When considering interventions to reduce cancer incidence, it is important to appreciate how relative and attributable risks reported in studies of risk factors relate quantitatively to absolute risk. In Sweden about 20% of oesophageal cancers can be attributed to low consumption of fruit and vegetables – a measure of attributable risk. Assuming dietary change reduces the risk, it would be necessary for more than 25,000 people to increase their dietary intake of fruit and vegetables to a moderate extent to prevent one case of oesophageal cancer per year – the change in absolute risk.⁶⁰ 2++

2.3 CHEMOPREVENTION

Observational studies indicate that use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) is associated with reduced oesophageal squamous and adenocarcinoma incidence⁶¹ and gastric cancer incidence.^{62,63} It is not clear whether the benefits of such treatment outweigh the risks. 2+
3

D Aspirin or NSAIDs should not be used for chemoprevention of oesophageal and gastric cancer.

Dietary supplementation with antioxidant vitamins and micronutrient minerals has been studied in populations with a high incidence of oesophageal and gastric cancer but benefit has not been proven.⁶⁴⁻⁶⁹ 3

3 Presentation and referral

3.1 UNCOMPLICATED DYSPEPSIA

In young patients with uncomplicated dyspepsia (*ie no alarm symptoms, see section 3.3*), oesophageal and gastric cancer is extremely rare. The SIGN guideline on dyspepsia has recommended that a non-invasive *Helicobacter pylori* test and treatment strategy is as effective as endoscopy in the initial management of patients under the age of 55 years presenting with uncomplicated dyspepsia.⁷⁰ Studies which support this policy fall into two categories:

- prospective randomised controlled trials of dyspepsia management comparing *Helicobacter pylori* test and treat versus prompt endoscopy⁷¹⁻⁷³
- retrospective cohort studies of gastric cancer patients, which demonstrate that the majority of young patients have alarm symptoms by the time of presentation.^{74,75}

The number of missed cancers in patients with uncomplicated dyspepsia is extremely low. Only 1–2% of patients presenting with symptoms of dyspepsia at endoscopy harbour malignancy.⁷⁶ Although dyspepsia is a common presenting symptom of early gastric cancer in the Far East, it is not clear if this is the case in the West. In some cohort studies uncomplicated dyspepsia or pain has been reported in no more than 5% of Western patients with upper gastrointestinal (GI) cancer.^{74,75,77} The vast majority of patients from these studies have advanced disease at presentation. Other cohort studies have reported a higher incidence of uncomplicated dyspepsia in upper GI cancer patients. In a UK study dyspepsia or pain was the presenting symptom in 17% of upper GI cancers.⁷⁸ In another case series the GP records of 685 upper GI cancer patients documented the absence of alarm symptoms (*see section 3.3*) at the initial presentation of 50% of patients.⁷⁹ A similar figure was found in a group of young gastric cancer patients in Italy with a significantly better survival compared to those patients presenting with alarm symptoms.⁸⁰

The decision as to when to refer patients with uncomplicated dyspepsia is contentious as a result of these conflicting observational studies, which are limited by their retrospective nature.

Relying solely on a clinical diagnosis of dyspepsia may lead to the misclassification of one third of patients with a major pathological lesion.⁷⁶ This suggests that patients with persistent or refractory symptoms should be referred for endoscopy.

The Department of Health in England has developed criteria for urgent investigation of suspected upper GI cancer.⁸¹ Uncomplicated dyspepsia in patients > 55 years of age is one of the recommended criteria but a recent clinical prediction model concludes that this is a poor predictor of cancer and is of limited value.⁸²

A prospective non-randomised study of the impact of open access endoscopy suggested an increase in early gastric cancer detection in a middle aged population of patients with dyspepsia. Subsequent studies have failed to demonstrate either earlier diagnosis or any survival benefit from open access endoscopy.⁸³

B A test and treat policy for *Helicobacter pylori* should be employed in the initial management of patients with uncomplicated dyspepsia.

C Irrespective of age, patients should be reviewed after *Helicobacter pylori* eradication treatment. For those with recurrent or persistent symptoms the need for further assessment, including endoscopy, should be considered.

3.2 SYMPTOMS OF GASTRO-OESOPHAGEAL REFLUX

Symptoms such as heartburn are extremely common in the general population. Cohort studies from North America demonstrate that reflux symptoms occur monthly in almost 50% of adults and weekly in 20%.⁸⁴ Indiscriminate referral of such patients to secondary care would be inappropriate. A cross-sectional observational study found that although increased referral of patients with reflux symptoms significantly increased the proportion of endoscopy positive gastro-oesophageal reflux disease, there was no significant increase in the detection of complications such as Barrett's, benign stricture or cancer.⁸⁵

2-

Several case control studies have demonstrated a positive association between reflux symptoms and risk of adenocarcinoma of the oesophagus, but the risk appears less with adenocarcinoma of the oesophagogastric junction.^{9,32,36,86,87} A Swedish case control study comparing patients newly diagnosed with adenocarcinoma of the oesophagus or oesophagogastric junction with patients with oesophageal squamous cancer and controls, found that among those with recurrent symptoms of reflux, compared to those without these symptoms, the odds ratio (OR) was 7.7 for oesophageal adenocarcinoma, increasing to 43.5 when symptoms were more severe and long standing (> 20 years). The association of reflux with cancer at the oesophagogastric junction was also weaker in the Swedish study.³² Hiatus hernia and reflux symptoms were associated with an OR of 8.11 in a population based study.⁸⁶

2+

Despite the association between reflux and oesophageal adenocarcinoma, there are major difficulties in using reflux symptoms as a marker for risk. A well conducted systematic review calculates that the cancer risk to any given individual over the age of 50 years, with reflux on a weekly basis, would still be extremely low and concludes that insufficient evidence exists to endorse routine endoscopy screening in patients with chronic gastro-oesophageal reflux symptoms.⁸⁴

1+

C In patients with gastro-oesophageal reflux symptoms, endoscopy with the intention of identifying cancer is not indicated unless an alarm symptom is also present.

3.3 ALARM SYMPTOMS

The classical 'alarm' symptoms that are associated with oesophageal and gastric cancer are dysphagia, vomiting, anorexia and weight loss or symptoms associated with GI blood loss. Presence of any of these symptoms is sufficient to prompt early endoscopy.

An editorial review on the value of alarm symptoms in identifying organic causes of dyspepsia, showed that dysphagia, vomiting and weight loss were present in 60–85% of patients with oesophageal cancer. Weight loss and anaemia are present in 60–70% and 20–40% of patients with gastric cancer respectively. The vast majority of patients from retrospective studies have advanced disease at presentation.⁸⁸

4

Alarm symptoms in patients with dyspepsia were evaluated in a prospective study comparing patients presenting with or without alarm symptoms. Over a three-year follow up period the presence of one or more alarm symptoms raised mortality rates significantly compared to the dyspepsia only group, but the observed increase in the development of GI cancer was not significant: OR = 1.9 (0.9-4.1). It was concluded that although the presence of alarm symptoms predicted a bad prognosis, the positive predictive value was low (4%) and a negative predictive value high (98%) with respect to cancer, reflecting a low incidence of the disease in the population at risk. This study supports the view that the majority of patients with alarm symptoms do not have cancer. It should be noted that GI diseases were diagnosed in relation to one third of those with alarm symptoms overall.⁸⁹

2+

In one study the use of scoring systems based on an assessment of patient characteristics and risk factors did not significantly improve upon referral to endoscopy based on classical alarm symptoms. The study concluded that the commonly accepted alarm symptoms were very useful predictors of malignancy.⁹⁰ Conversely, an American multicentre prospective study of 3,815 patients found that age and the presence of alarm symptoms were ineffective predictors of endoscopy findings among patients with dyspepsia. Although their results lent support to age, anaemia and bleeding symptoms as independent predictors of endoscopic findings, the predictive accuracy was very low with particular reference to cancer.⁹¹ 2+

Although cancer risk may be small, patients with alarm symptoms and dyspepsia have a higher probability of organic disease than patients with dyspepsia alone.⁸⁸ 4

A British study has validated a clinical prediction model based on alarm symptoms for rapid access endoscopy. Dysphagia, weight loss and age > 55 years were significant predictors of cancer but uncomplicated dyspepsia in patients > 55 years of age was a negative predictive factor. Ninety two per cent of cancer patients would be selected for fast-track investigation based on a model incorporating dysphagia or weight loss at any age or dyspepsia > 55 years associated with any of the other recognised alarm features.⁸² 2+

B Patients presenting with any of the following alarm symptoms should be referred for early endoscopy:

- dysphagia
- recurrent vomiting
- anorexia
- weight loss
- gastrointestinal blood loss.

3.4 DELAY IN DIAGNOSIS

3.4.1 DURATION OF SYMPTOMS

Symptoms indicative of gastric or oesophageal cancer may have been present for variable amounts of time, ranging from one week to three years prior to diagnosis.⁷⁸ The duration of symptoms before diagnosis does not predict either tumour resectability or subsequent survival.^{78-80,92,93} In the SAGOC audit, a longer interval between symptom onset and diagnosis, which might be interpreted as delay in diagnosis, was associated with better survival.² 2++
2+
3

3.4.2 PATIENT DELAYS

Although many patients are quick to seek medical advice for their symptoms, subtle symptoms may be overlooked. Approximately 30% of patients with oesophageal and gastric cancers wait for more than four months after the onset of symptoms before seeking medical attention. No difference between socioeconomic groups in the time taken to seek medical attention has been found. Many patients could not be sure of the length of time of their symptomatology.² Patients may self administer histamine₂ receptor antagonist drugs or antacids for several months without seeking formal medical advice.⁷⁹ 2+
3

3.4.3 GENERAL PRACTITIONER DELAYS

Careful history taking by the GP can help identify patients requiring urgent referral for endoscopy.

In one retrospective cohort study (n = 685), prior antisecretory drug therapy was associated with delayed diagnosis of upper gastrointestinal adenocarcinoma by 17.6 weeks (mean) irrespective of presenting symptoms. There was no effect on tumour stage at diagnosis or on survival.⁷⁹ 3

Adoption of a "test and treat" strategy for *Helicobacter pylori* instead of endoscopy may mean that a diagnosis of gastric or oesophageal cancer is delayed. The efficacy and acceptability of the "test and treat" strategy depends on GP awareness, vigilance, and thoroughness of follow up after *Helicobacter pylori* eradication therapy.⁷⁰ 4

3.4.4 HOSPITAL WAITING LIST DELAYS

The SAGOC audit showed that 18.8% of patients in Scotland waited more than four weeks for their first diagnostic examination.² The use of open-access endoscopy may reduce delay in diagnosis compared with standard referral patients with oesophageal cancer, but not for patients with gastric cancer.⁷⁸ Implementation of clinical prediction models based on “at risk” symptoms (see section 3.3) should improve the patient journey for gastric and oesophageal cancer sufferers and their carers.⁸²

2+

The evidence from the observational studies cited above indicates that delays in diagnosis are unimportant with respect to tumour resectability or a patient’s subsequent survival. Delays after referral for investigation are likely to be associated with increased patient anxiety.²

- Prompt investigation and assessment of patients referred with symptoms suggestive of oesophageal or gastric cancer are desirable in order to minimise the period of anxiety and uncertainty about diagnosis for the patients, their families and carers.

4 Diagnosis

Diagnosis of oesophageal or gastric cancer on clinical grounds alone is unreliable.^{89,91} Two investigative methods are routinely available: contrast radiology (barium swallow/meal) and upper GI endoscopy (UGIE). The choice will depend on availability, ease of access, waiting times and patient preference.

4.1 BARIUM RADIOLOGY (BARIUM SWALLOW/MEAL)

Barium studies are safe, non-invasive, do not require sedation and are widely available. In the SAGOC study 29% of patients with oesophageal or gastric cancer had initial barium studies prior to referral to hospital.² Although barium studies are sensitive for the diagnosis of malignancy, in Western countries radiology appears to be less sensitive than endoscopy for the diagnosis of early malignancy (cancer in situ and T1 cancers).⁹⁴ Barium studies cannot reliably diagnose premalignant lesions including dysplasia.⁹⁵

3

4.2 UPPER GI ENDOSCOPY

Upper GI endoscopy is sensitive for the diagnosis of oesophageal and gastric cancers, allows biopsy and avoids the use of ionising radiation.⁹⁶ Procedure completion rates are high and UGIE can often be undertaken without intravenous sedation. Tumours can be accurately localised and mapped. The complication rate for diagnostic endoscopy is very low. Procedure-related mortality is approximately 1 in 10,000 and significant complications (mostly sedation related) occur in approximately 1 in 1,000 cases. Minor complications such as sore throat occur in up to 10% of cases.⁹⁷

2+

Flexible UGIE is safer than rigid oesophagoscopy for the diagnosis of oesophageal cancer.⁹⁸

4

UGIE is widely available and almost universally used in Scotland in the diagnosis of upper GI pathology, including neoplasia.²

3

There is no definitive evidence to support the superiority of one modality over the other in the initial diagnosis of oesophageal and gastric cancer but UGIE provides a means of obtaining histological confirmation and minimises duplication of tests since almost all patients who have the diagnosis made by barium studies will subsequently have UGIE.² There is some evidence that patients prefer UGIE over barium studies.⁹⁹

3
2+

C Flexible upper GI endoscopy is recommended as the diagnostic procedure of choice in patients with suspected oesophageal or gastric cancer.

4.2.1 CHROMOENDOSCOPY

Spraying stains onto the mucosa during UGIE may enhance the detection of small, subtle lesions and/or dysplasia. The stain used depends on the mucosa being examined. The most commonly used stains and lesions targeted include Lugol's iodine for dysplastic and malignant squamous epithelium of the oesophagus,¹⁰⁰ methylene blue for enhancing identification of specialised intestinal metaplasia in Barrett's epithelium¹⁰¹⁻¹⁰³ and indigo carmine for early cancer in gastric mucosa.¹⁰⁴

3

D Routine use of chromoendoscopy during upper GI endoscopy is not recommended, but may be of value in selected patients at high risk of oesophageal or gastric malignancy.

4.3 HISTOLOGICAL DIAGNOSIS

4.3.1 BIOPSY TECHNIQUE

The accuracy of diagnosis of malignancy increases with the number of biopsies taken. In one prospective study, the diagnostic yield of malignancy in oesophageal cancer was 95% with four biopsies and rose to 100% if eight biopsies were taken. These results were unrelated to tumour site or type. Cytology may complement histology but when used alone is no better than biopsy.¹⁰⁵

In Barrett's oesophagus the detection rate of dysplasia is determined by the biopsy protocol used.^{37,42} The majority of case series which report detection of early stage cancers employ structured protocols with at least four quadrant biopsies every two centimetres along the Barrett's segment.^{6,38} Results from case series using random or non-structured biopsy protocols are generally poor.^{106,107}

2+

C A minimum of eight biopsies should be taken to achieve a diagnosis of oesophageal malignancy.

C In patients with Barrett's oesophagus there should be a structured biopsy protocol with quadrantic biopsies every two centimetres and biopsy of any visible lesion.

4.3.2 HISTOPATHOLOGY

The diagnosis of malignancy should, whenever possible, be confirmed pathologically.

Invasive malignancies should be reviewed by a specialist GI pathologist at an appropriate multidisciplinary meeting.

There is consistent evidence of significant inter- and intra-observer variation among Western pathologists in the diagnosis of dysplasia and intramucosal cancer in patients with oesophageal and gastric cancer. This may have a considerable clinical impact on diagnosis and management in this group of patients.¹⁰⁸⁻¹¹⁰

Well designed studies employing the Vienna classification (see *Annex 1*) show that the consistency of dysplasia grading is reasonably good in relation to high grade dysplasia /intramucosal adenocarcinoma and 'no dysplasia' but less reliable for grades in between.^{108,111} There is little data on the reliability of the diagnosis of intramucosal and invasive adenocarcinoma. Non-specialist pathologists may overdiagnose low-grade dysplasia in particular. The accuracy of biopsy interpretation in Barrett's oesophagus is improved when the reporting pathologist is aware of clinical background and endoscopic findings.^{109,110}

2+

C Pathologists should follow the revised Vienna classification for reporting dysplasia.

C Where radical intervention is contemplated on the basis of high grade dysplasia or early adenocarcinoma the diagnosis should be validated by a second pathologist experienced in this area and further biopsies should be taken if there is uncertainty.

C Evaluation of suspected high grade dysplasia in Barrett's oesophagus biopsies should be undertaken with knowledge of the clinical and endoscopic background and biopsies should be reviewed at a multidisciplinary meeting with access to the clinical information.

5 Assessment and staging

5.1 STAGING MODALITIES AND TECHNIQUES

Patients are staged using the tumour, nodes, metastases (TNM) staging classification. Definitions of T, N and M stages for cancers of the oesophagus, oesophagogastric junction and stomach are from the 6th edition of the International Union Against Cancer (UICC) Classification of Malignant Tumours (see Annex 2).¹¹² The key staging techniques are computerised tomography (CT), endoscopic ultrasound (EUS) and laparoscopy. Other modalities include magnetic resonance imaging (MRI), positron emission tomography (PET) and bronchoscopy.

5.1.1 COMPUTERISED TOMOGRAPHY

High quality contrast enhanced computerised tomography is the most accurate, widely used, non-invasive modality for detecting distant metastases. Contrast enhanced CT identifies those patients with advanced metastatic disease who will not require further staging investigations.⁹⁹ Optimum detection of metastases occurs when the liver is imaged in the portal venous phase.¹¹³ There is evidence that pelvic CT is not required in the staging of oesophageal cancer.¹¹⁴ No evidence was identified on the value of pelvic CT in patients with gastric cancer.

2++
4

B In patients with oesophageal or gastric cancer CT scan of the chest and abdomen with intravenous contrast and gastric distension with oral contrast or water should be performed routinely. The liver should be imaged in the portal venous phase.

5.1.2 ENDOSCOPIC ULTRASOUND

There are many diagnostic studies of variable standard assessing the efficacy of EUS in the staging of oesophageal or gastric cancer. Most are consistent in their findings and indicate that endoscopic ultrasound is more accurate than incremental CT for locoregional staging of oesophageal cancer (ie N and particularly T stage).¹¹⁵ Although no randomised trials comparing EUS with helical or multidetector CT have been published, two prospective, blinded studies have demonstrated the superiority of EUS over helical CT for T and N staging.^{116,117} EUS accuracy is lower in assessment of non-traversable and oesophagogastric junction cancers and data regarding the utility of high frequency catheter probes do not support their use in routine staging.¹¹⁵

1+
2++

EUS also allows fine needle aspiration (FNA) of suspicious lymph nodes. This improves the accuracy of nodal staging and limited evidence suggests this impacts on treatment decisions.¹¹⁶

2++

In the staging of gastric cancer, other modalities such as laparoscopy are often used which may obviate the need for EUS.

B Patients with oesophageal or oesophagogastric junction cancers who are candidates for any curative therapy should have their tumours staged with endoscopic ultrasound +/- fine needle aspiration.

5.1.3 LAPAROSCOPY, CYTOLOGY AND ULTRASOUND

Laparoscopy can help in the staging of oesophageal tumours extending into the proximal stomach and in staging of gastric tumours.¹¹⁸⁻¹²¹ There are inconsistent data regarding the added benefit from peritoneal cytology.^{118,121,122} There are insufficient data to confirm benefit from laparoscopic ultrasound.^{123,124}

2+
2-

C Laparoscopy should be considered in patients with oesophageal tumours with a gastric component, and in patients with gastric tumours being considered for surgery where full thickness gastric wall involvement is suspected.

5.1.4 MAGNETIC RESONANCE IMAGING

MRI is as accurate for TNM staging as CT^{81,125,126} but is less accurate for the detection of pulmonary metastases.^{127,128} There is no anatomical area where MRI is superior to CT.¹²⁹

2⁺⁺
2⁺

C MRI should be reserved for those patients who cannot undergo CT, or used for additional investigation following CT/EUS.

5.1.5 BRONCHOSCOPY

Four diagnostic studies provide weak evidence that bronchoscopy combined with bronchoscopic ultrasound (BUS) and/or biopsy may be of value in assessing tracheobronchial invasion.¹³⁰⁻¹³³

3

D Bronchoscopy +/- BUS +/- biopsy should be undertaken in patients with clinical or imaging features suspicious of tracheobronchial invasion.

5.1.6 THORACOSCOPY

One prospective study suggests that thoracoscopy is the most accurate modality to detect positive mediastinal lymph nodes in oesophageal cancer but there are insufficient comparison data with other modalities such as EUS to support this.¹³⁴

3

D Thoracoscopy may be considered for patients where a tissue diagnosis of suspicious nodes (not possible by either EUS or CT guided techniques) is required to determine optimum management.

5.1.7 POSITRON EMISSION TOMOGRAPHY

A meta-analysis of small diagnostic studies concluded that PET offers no significant improvement in staging accuracy in patients with oesophageal cancer compared with standard imaging techniques.¹³⁵ In small diagnostic studies PET has not been found to improve diagnostic accuracy in the staging of gastric cancer.^{136,137}

2⁺⁺

C PET is not routinely indicated in the staging of oesophageal and gastric cancers.

5.1.8 BONE SCAN

No evidence has been identified on the routine use of bone scanning in the staging of oesophageal or gastric tumours.

5.1.9 NECK IMAGING

In one study ultrasound of the neck demonstrated histologically confirmed malignant nodes in 28% of patients who had no clinically palpable nodes. Neck CT was only performed in patients who had cervical or upper thoracic tumours. No comparison was made between CT and neck ultrasound (US) regarding relative accuracy.¹³⁸

3

D Neck imaging either by US or CT is recommended as part of the staging of oesophageal cancer.

5.2 IMPLICATIONS OF TUMOUR STAGE

One of the major findings of the SAGOC audit was that patients were under-staged preoperatively and curative surgery was attempted too often. Forty per cent of patients in whom the preoperative intention was a curative resection subsequently had a palliative operation according to the surgeon's opinion postoperatively. As a result there were many incomplete resections and recurrence of tumour within 12 months and a one year postoperative survival of only 53%.²

5.2.1 TUMOUR STAGE, TREATMENT AND SURVIVAL

Evidence from multiple cohort studies reports consistent results in patients who have undergone surgical resection.

For patients with gastric or oesophageal cancer, tumour stage at diagnosis is the main determinant of survival. Lymph node involvement is the most important single factor, followed by T stage.¹³⁹⁻¹⁴³

In patients with oesophageal cancer, the presence of involved nodes reduces five year survival from 60-80% to approximately 25%.¹³⁹ The presence of more than four involved nodes or M1a node involvement is associated with significantly reduced survival, although it does not necessarily preclude long term survival following resection.¹⁴⁴ Long term survival is not seen in patients with junctional cancers who have cervical nodal disease or nodal metastases in three body compartments (neck, mediastinum and abdomen).¹³⁹

2++

In patients with gastric cancer both the number of involved nodes and the ratio of involved to uninvolved nodes significantly influence long term outcome.^{145,146} T stage is the most significant factor in node negative cases.¹⁴⁷

In patients with oesophageal cancer preoperative identification of lymph node involvement by EUS is associated with a poor prognosis.¹⁴⁸

3

Selected patients with T4 gastric cancer in the absence of extensive lymph node involvement can have long term survival (five years and over) following surgical resection.^{149,150}

3

The patients most likely to benefit from curative treatment are those without distant metastases and with limited lymph node involvement. Long term survival is possible in highly selected patients with more advanced disease but the majority of patients in this category will survive for less than two years following resection.

B Patients with gastric or oesophageal cancer should undergo careful preoperative staging to enable targeting of potentially curative treatment to those likely to benefit.

B Patients with gastric or oesophageal cancer who have distant metastases or patients with oesophageal cancer who have metastatic lymph nodes in three compartments (neck, mediastinum and abdomen) on preoperative staging are not candidates for curative treatment.

C When M1a nodal involvement in oesophageal cancer, or extensive lymphadenopathy in any cancer, is identified on preoperative staging, the anticipated poor prognosis should be carefully considered when discussing treatment options.

Where there is clear evidence of incurable disease following staging, attempts at resection should be avoided.

5.2.2 TUMOUR STAGE AND QUALITY OF LIFE

There is no evidence directly addressing the influence of tumour stage on quality of life in patients with oesophageal cancer. Surgery results in a reduction in quality of life which only returns to preoperative levels in patients surviving more than two years. In these patients quality of life improves after three to four months and approaches preoperative levels at around nine months.¹⁵¹

3

In patients with gastric cancer, one study demonstrated no relationship between tumour stage and quality of life following surgery.¹⁵²

D The possibility of reduction in quality of life after surgery should be considered when discussing treatment options, particularly when preoperative staging suggests that surgery would be unlikely to be curative.

5.3 ASSESSMENT OF PREOPERATIVE FITNESS

Of all patients with oesophageal and gastric cancers who are surgically assessed, over half (57%) are rejected for surgery because they are considered insufficiently fit.¹⁵³ In those who have surgery, respiratory (20-41%) and cardiac (11-16%) complications are the major causes of postoperative mortality.^{2,153} Complications can be reduced by removing those patients at greatest risk from the surgical cohort.¹⁵⁴ This is most frequently achieved by exercising clinical judgement and there is evidence that this is predictive of in-hospital mortality.¹⁵³ The more objective POSSUM (physiological and operative severity score for the enumeration of mortality and morbidity) scoring system is also predictive of in-hospital death. Both POSSUM and ASA grade (American Society of Anesthesiologists) independently predicted medical complications.¹⁵³

2+

Scoring systems for risk prediction specifically for patients with oesophageal cancer have been developed. Use of a composite scoring system based on general performance status as well as cardiac, hepatic and respiratory function has been shown to reduce postoperative mortality from 9.4% to 1.6% but the system relied on subjective judgement and appeared cumbersome.¹⁵⁴ A simpler but unvalidated scoring system based on age, spirometry and performance status predicted an incrementally increasing risk of respiratory and cardiac complications although it did not predict postoperative mortality.¹⁵⁵

2+

A Japanese study found no association between preoperative cardiac or hepatic dysfunction and the development of postoperative complications, but respiratory dysfunction, FVC (forced vital capacity) < 80% or FEV1 (forced expiratory volume in first one second) < 70%, did predict complications.¹⁵⁶ Another Japanese study did not find routine pulmonary function tests useful but found that expired gas analysis during exercise predicted cardiopulmonary complications.¹⁵⁷ This measure of cardiopulmonary reserve is not routinely available. In an American study of high-risk surgical patients, symptom-limited stair climbing predicted postoperative complications.¹⁵⁸

2+
3

The role of dynamic testing of cardiac function has not been addressed in patients with oesophageal and gastric cancers.

B All patients being considered for surgery should undergo careful assessment of fitness with emphasis on performance status and respiratory function.

5.4 PATHOLOGICAL STAGING OF RESECTED SPECIMENS

SAGOC illustrated the variability in the reporting of the pathology of resection specimens from patients with oesophageal and gastric carcinomas.²

Accurate completion of pathology reports is essential to ensure accurate pathological staging (for comparison with clinical staging), to inform assessment of prognosis, to indicate the completeness and adequacy of resection and to assist in audit.

5.4.1 IMPORTANT PATHOLOGICAL PARAMETERS

Resection specimens need to be dissected carefully for accurate tumour staging. Tumour stage correlates with prognosis (see section 5.2). The Royal College of Pathologists (RCP), in its standards and minimum data sets has identified important parameters.¹⁵⁹ The RCP standards also give information on the ideal preparation and dissection methods for resection specimens and the information which should be recorded for each resection (see Annexes 3 and 4).

The following parameters have been identified as important in the RCP standards:

- **Oesophageal, and junctional type I and II cancers** - extent within the wall, longitudinal margins, vascular invasion and total number of lymph nodes and number and sites in which there is metastatic tumour. The latter is important to identify M1 nodes as these are associated with a poor prognosis.^{145,146,159}
- **Gastric, and junctional type III cancers** - extent within wall (particularly serosal invasion) and involvement of other organs; and numbers of lymph nodes in total and with metastasis, respectively. Prognosis is associated more with the number of lymph nodes involved rather than their location, with involvement of > 6 lymph nodes associated with a poorer prognosis.^{144,159}

2++

In pathological reporting of resection specimens of colorectal cancer the use of template proformas improves the recording of basic information.^{160,161} This finding is applicable to gastric and oesophageal cancer reporting.

1+
2+

B Resection specimens of oesophageal and gastric cancer resections should be reported according to, or supplemented by, the Royal College of Pathologists' minimum data sets.

6 Treatment principles

6.1 INTRODUCTION

The choice of treatment for patients with oesophageal or gastric cancer depends on the stage of the disease, and on the condition and wishes of the patient. Patients with resectable lesions may be unfit for surgery or potentially curative chemoradiotherapy by virtue of significant comorbid disease (see section 5.3). The patient's preoperative status and comorbidity are strong predictors of outcome. The management of all patients should be discussed in an appropriate multidisciplinary meeting (MDM) where all staging and other relevant information is available to all members of the team. Patients should be informed of the treatment options available (surgery, chemotherapy or radiotherapy), and these should be evaluated in terms of risks and benefits.¹⁵¹

- The management of all patients who are diagnosed with gastric or oesophageal cancer, should be discussed within a multidisciplinary forum.

6.2 INFORMATION, COMMUNICATION AND SUPPORT

Stress associated with the diagnosis and treatment of cancer can cause significant psychological morbidity. There is some evidence that providing emotional, spiritual and practical support may have a positive effect on patients' well-being.¹⁶² Giving better information and taking time to explain and understand patients' concerns can result in decreased psychological distress for patients and have a positive impact on patients' quality of life.¹⁶³ Obtaining support from national and local support groups can improve a patient's ability to cope and information relating to these support services should be made readily available.¹⁶⁴

- Health professionals providing care and treatment for patients with oesophageal or gastric cancer should seek appropriate training in communication skills.

D Information relating to local and national support services should be made available to both patients and carers.

- Patients should be given clear information relating to the potential risks and benefits of treatment.

6.2.1 ROLE OF CLINICAL NURSE SPECIALIST

Clinical nurse specialists (CNS) have a major role to play in improving patients' quality of life through provision of ongoing support, advice, information and education for patients and their carers throughout their illness. They also have a role in managing continuity between primary and secondary care.^{165,166}

- All patients newly diagnosed with oesophageal or gastric cancer should have access to a clinical nurse specialist for support, advice and information and to facilitate timely communication with primary care.

6.3 ONGOING SUPPORT/FOLLOW UP

Patients who have undergone apparently curative resection for oesophageal or gastric cancer are followed up for four reasons:⁹⁸

- to detect disorders of function, either related to recurrent disease or benign complications of treatment
- to assess nutritional status and manage nutritional problems
- to provide psychosocial support for patients and their families, including appropriate medical measures in liaison with palliative care
- to facilitate audit of treatment outcomes.

4

Follow up can be done by monitoring symptoms and signs including weight loss, and by providing ongoing support. The frequency of follow up should be more intensive initially to detect complications and ensure nutritional balance. The length of follow up is determined by the individual patient's need for ongoing support, and by the period to recurrence of these cancers. Based on the survival pattern of these cancers, most of the recurrences are within five years.

No evidence has been identified to support regular imaging or measurement of serum tumour markers in the follow up of patients with gastro-oesophageal cancer outside clinical trials.

D Follow up of patients with oesophageal or gastric cancer should monitor symptoms, signs and nutritional status.

- Patients who have undergone curative resection for oesophageal or gastric cancer should undergo formal follow up in order to detect disorders of function either related to recurrent disease or any factors affecting quality of life.

7 Surgery

7.1 GENERAL PRINCIPLES

Surgical treatment remains the mainstay for cure and is considered for all patients with potentially curable oesophageal and gastric cancer who are fit for major surgery (see section 5.3). The therapeutic options for patients not suitable for surgery should be considered by a multidisciplinary team. The aim of surgical resection is to achieve complete removal of the tumour with histologically confirmed tumour free (R0) surgical margins which usually requires proximal and distal margin clearance of at least 5-10 cm. The extent of resection must also take into account factors such as:¹⁶⁷

- site of tumour
- submucosal spread as assessed by endoscopic ultrasonography
- histological type of tumour
- presence of satellite nodules or Barrett's metaplasia
- proximity to cricopharyngeus (and hence necessity to remove the larynx).

4

Circumferential margin clearance (> 1 mm) is a strong indicator for a longer disease-free interval for patients with oesophageal cancer.¹⁶⁸ Where possible adjacent structures (such as the crura of the diaphragm) should be resected en-bloc with the tumour.

2+

Radical surgery should be recommended for patients with T1, T2 and T3 tumours with a relatively low lymph node burden who are sufficiently fit to tolerate the procedure (see section 5.2.1). Patients with T4 disease involving structures that cannot easily be resected and those with distant metastases should not undergo surgery.¹⁵¹

7.2 SERVICE DELIVERY

7.2.1 INTRODUCTION

Several studies report an association between increasing surgeon or hospital volume and improved outcomes in relation to oesophageal and gastric resection. Interpretation of these studies is difficult. Many of the studies are retrospective, have small numbers and the definitions of high and low volume centres vary. Several have been based only on hospital coding systems and have not taken into account case mix and comorbidity. There has also been lack of clarity in studies between mortality rates attributed to institutions and those associated with individual surgeons, particularly where institutions have more than one unit undertaking oesophageal or gastric surgery. These complexities may explain the range of results reported which include small volume single surgeon units with excellent results and larger volume units reporting poor perioperative mortality.

7.2.2 PERIOPERATIVE MORTALITY AND VOLUME OF WORK

Two systematic reviews which accounted for case mix and small patient numbers, and excluded single institution studies, demonstrated higher volume centres to be associated with reduced mortality in the treatment of a number of conditions including oesophagogastric cancer.^{169,170} The first included five studies on oesophageal and gastric resections and found a median absolute difference in in-hospital mortality rate for high volume centres compared to low volume centres of 12% for oesophagectomy and 6.5% for gastrectomy. Centres defined as high volume in this review had a median of 30 patients per year (range 11-200), low volume centres had a median of five resections per year (range 5-10). The second review analysed the results of 10 studies and found that all but one demonstrated a volume effect for oesophageal resection, mainly in relation to hospital volume but with some evidence for significant effects associated with individual surgeon volume. Three studies were common to both reviews.

2+

Studies show a varying degree of volume effect for both resections.^{153,169-172} One study reported statistically significant reductions in in-hospital mortality with increasing numbers of resections.¹⁷³

2+

Two studies reported inconsistent volume results.^{172,174} One study found a trend towards lower operative risks at high volume hospitals which was statistically significant for oesophageal cancer resections but not for gastric cancer resections.¹⁷⁵ An association between increased volume and improved long-term survival was reported in one study.¹⁷⁶

2+

Most of these studies concentrated on comparing low volume and high volume providers. The most significant differences tended to be between very low volume centres and very high volume centres. One study has compared low (1-10 resections per annum), medium (11-20 resections per annum) and high volume (> 50 resections per annum) institutions in relation to oesophagectomy and reported an inverse relation between hospital mortality and hospital volume.¹⁷¹ Another study of oesophageal resections compared low volume hospitals (< 3 resections per annum) with medium (3-5 resections per annum), high (6-16 resections per year) and very high volume hospitals (> 16 resections per annum) and reported significant differences between the very high and the low volume hospitals, where there was an absolute mortality risk difference of 8.1%.¹⁷⁷

2+

In a large retrospective study examining mortality associated with major cardiovascular procedures and cancer resections, surgeon volume was inversely related to perioperative mortality, irrespective of whether the hospital was a low or high volume provider. This suggests that associations between hospital volume and perioperative mortality are largely mediated by surgeon volume.¹⁷⁸ In another retrospective cohort study, 30 day mortality rate decreased by 40% for each increase of 10 patients in individual annual case loads for oesophageal cancer and by 41% for each increase of 10 patients in gastric cancer.¹⁷⁶

2+

Although the technical results of the operation are important and have a significant impact on both in-hospital mortality and long term survival,¹⁷⁹ the benefits associated with high volume centres probably also relate to the other disciplines, protocols and resources involved in the overall care of these patients.

7.2.3 CONCLUSION

There is good evidence that patients who require oesophageal or gastric resection should not be operated upon by individual surgeons performing small numbers of procedures. Surgeons undertaking oesophagogastric cancer surgery should work within high volume units and perform large numbers of procedures. There is some evidence that the advantages associated with higher volume hospitals and operators continue as the number of procedures increase.^{171,176} Two UK guidelines for the management of patients with oesophagogastric cancer have recommended that surgery should be undertaken in regional specialist centres performing high volume surgery. These guidelines were based on clinical and resource related issues.^{98,180}

2+
1+
4

B Oesophageal and gastric cancer resectional surgery should be carried out in high volume specialist surgical units by frequent operators.

7.3 TYPE OF OPERATION

7.3.1 OESOPHAGUS AND OESOPHAGOGASTRIC JUNCTION

Type I tumours are treated using a subtotal oesophagectomy along with a sleeve resection of the gastric cardia and lesser curve in addition to the lymph nodes around the left gastric pedicle.¹⁶⁷ Type III tumours are treated by total gastrectomy with resection of the distal oesophagus.¹⁶⁷ There are no studies or guidelines relating to the management of tumours straddling the oesophagogastric junction (Type II). The decision for surgery should be made on a case-by-case basis, influenced by possible nodal spread, the presence of Barrett's metaplasia and the possibility of submucosal extension into the stomach or oesophagus.¹⁶⁷ Only one randomised study has compared an extended transthoracic resection versus a limited transhiatal resection for adenocarcinoma of the oesophagus. Perioperative morbidity was higher in patients undergoing extended transthoracic resection but there was no significant difference in in-hospital mortality. The difference in survival was not significant although there was a trend to improved survival at five years, with 39% surviving in the extended thoracic group compared to 29% in the transhiatal group.¹⁸¹

4
1+

7.3.2 STOMACH

The aim of resection is wide clearance of the tumour along with adjacent lymph nodes.¹⁸² For proximal tumours this will usually necessitate total gastrectomy. For distal tumours the proximal stomach can be spared without compromising either perioperative mortality or survival.¹⁸³ 1+

There is insufficient evidence to recommend laparoscopic and thoracoscopic approaches for the surgical management of oesophagogastric cancer although some early reports suggest a role for these techniques in both oesophageal and gastric resection.¹⁸⁴⁻¹⁸⁶ 1+
2+

B **Surgery for oesophageal or gastric cancer should be aimed at achieving an R0 resection (proximal, distal and circumferential margin clearance).**

Laparoscopic and thoracoscopic techniques should only be carried out by experienced surgeons within specialist units as part of a controlled prospective study with full informed consent and local clinical governance committee support.

7.4 RECONSTRUCTION

7.4.1 AFTER OESOPHAGECTOMY

The commonest method for reconstruction after oesophagectomy is to use the stomach as a conduit and the commonest route is the posterior mediastinum. When the stomach is unsuitable or unavailable either the colon or jejunum can be used. A meta-analysis of randomised controlled trials found no significant difference in outcomes between the anterior or posterior mediastinal route.¹⁸⁷ There was a trend to fewer complications associated with the posterior route, but the number and size of studies analysed was small. There is no evidence to support a difference in outcome between a cervical and a thoracic anastomosis.¹⁸⁸ A meta-analysis of randomised trials found a slightly higher operative mortality following stapled anastomosis compared with hand sewn anastomosis after oesophagectomy.¹⁸⁹ Although this finding was statistically significant it was difficult to explain the reasons behind it. The addition of a drainage procedure (pyloroplasty) reduces the occurrence of early postoperative gastric outlet obstruction but has little effect on other early and late patient symptoms.¹⁹⁰ 4
1-
1+

B **Following oesophagectomy, the route of reconstruction and potential use of pyloric drainage procedure should be determined by the surgeon based on their individual experience.**

7.4.2 AFTER GASTRECTOMY

Reconstruction after total gastrectomy can be with or without pouch formation and with or without maintenance of duodenal passage. The evidence suggests that pouch procedures may be associated with a higher early weight gain and some improvement in long term quality of life. Preservation of duodenal transit offers little clinical benefit.¹⁹¹ 1+

B **Consideration should be given to pouch formation after total gastrectomy.**

7.5 LYMPHADENECTOMY

7.5.1 OESOPHAGUS

Prognosis after oesophagectomy is significantly reduced by the presence of four or more involved lymph nodes.^{139,144} Local disease control may be improved with radical lymphadenectomy and better staging information is obtained.¹⁴⁴ Good long term results from a two-field lymphadenectomy with subtotal oesophagectomy have been reported for patients with oesophageal cancer but there have been no randomised trials demonstrating improved survival.¹⁹² In patients with squamous cell cancer of the oesophagus extended cervical and superior mediastinal lymphadenectomy does not demonstrate significant improvement in five year survival compared with standard resection and may increase pulmonary complications.¹⁹³ 3
2+
1+

D Two-field lymphadenectomy should be considered during oesophagectomy to improve staging and local disease control.

B Routine extension of lymphadenectomy into the superior mediastinum or neck should not be carried out.

7.5.2 STOMACH

Meta-analysis of two multicentre randomised comparisons of limited (D1) versus extended (D2) node dissection trials found no advantage with regard to cure following D2 resection.¹⁹⁴ The number of patients operated on by each centre was small and the morbidity and mortality in the D2 groups was high in comparison with similar studies.¹⁸³ The mean number of lymph nodes resected in the D2 group in both studies was significantly lower than the 26 nodes or more anticipated following a formal D2 resection, suggesting patients may have undergone a less extensive or less meticulous lymphadenectomy. Long term subgroup analysis of one of the studies suggested that for patients with N2 disease an extended lymph node dissection may offer cure but it remains difficult to identify patients who have N2 disease preoperatively or intraoperatively.¹⁹⁵

1++
1+

In a single centre randomised study from the UK, a modified D2 gastrectomy without pancreatico-splenectomy improved survival twofold for patients with stage II and III gastric cancer, without significantly increasing morbidity and mortality when compared with a D1 gastrectomy.¹⁹⁶

1+

A large randomised study (n=615) from Italy comparing total with subtotal gastrectomy with D2 resection in all patients demonstrated increased five year survival with increased lymphadenectomy up to a maximum of 25 nodes, above which survival remained stable.¹⁸² Survival decreased with increasing number of metastatic lymph nodes, this effect plateauing at 20 nodes.

1+

Increasing the extent of resection for gastric cancer involving D3 and D4 lymphadenectomies is associated with increasing morbidity and no significant benefit to long term survival.^{197,198} The additional resection of the spleen and pancreas appears to be the cause of most of the significant increase in complications associated with an increased extent of resection in gastric cancer.¹⁹⁹ A large randomised study comparing D2 total gastrectomy with or without splenectomy demonstrated increased postoperative morbidity (but not mortality) and no long term survival advantage for those undergoing more radical surgery.²⁰⁰

1++
1+
4

B D2 lymphadenectomy, with a minimum of 25 lymph nodes removed, should be considered for patients undergoing gastrectomy. Routine resection of additional organs (*spleen and pancreas*) during gastrectomy is not recommended.

7.6 ANAESTHETIC MANAGEMENT

The incidence of perioperative mortality following surgery for oesophageal or gastric cancer ranges from below 5% to 20% and above.²⁰¹⁻²⁰³

The National Confidential Inquiry into Perioperative Deaths suggests improvements in outcome after oesophagectomy may be achieved by careful case selection and perioperative management by an anaesthetist experienced in the use of double lumen endotracheal (endobronchial) tubes and one-lung anaesthesia.²⁰¹

3

Advanced age and chronic respiratory disease are associated with mortality after oesophagectomy.¹⁵² Factors associated with the development of adult respiratory distress syndrome (ARDS) after oesophagectomy include the duration of surgery and one-lung ventilation, intraoperative cardiorespiratory instability and the need for blood and fluid replacement.²⁰⁴

2++
3

The amount of intraoperative fluid the patient receives during major surgery may influence outcomes. Fluid therapy aimed at unchanged body weight reduces complications after elective colorectal surgery^{205,206} and can be assumed to apply after oesophagogastric surgery.

1+
4

Appropriate postoperative analgesia is an important component of postoperative care for patients undergoing oesophagectomy or gastrectomy. Although the use of epidural analgesia does not in itself contribute to a reduction in operative mortality,²⁰⁷⁻²⁰⁹ the perioperative use of epidural analgesia is considered a core component of perioperative management by both physicians and patients.²¹⁰ Trials of epidural analgesia consistently demonstrate superior analgesia when compared to conventional parenterally administered narcotic techniques.²¹¹ | 1+
4

D The routine use of epidural analgesia is recommended in gastric and oesophageal cancer surgery.

Postoperative care in a high dependency or intensive care unit is essential for the postoperative management of patients undergoing oesophagectomy. There is no prospective data available to recommend either a short period of postoperative ventilation (up to 20 hours) or early extubation in theatre or the recovery room. Audit data show the two practices to be of equal merit.²¹²⁻²¹⁴ | 3

7.7 PERIOPERATIVE NUTRITIONAL STATUS

The majority of patients with gastric and oesophageal cancer present with obstructive symptoms. These can lead to nutritional problems and patients can become severely nutritionally debilitated. The type of procedure performed may also affect the nutritional management of the patient. Nutritional screening can identify those with current problems and when nutritional screening is reviewed, can detect nutritional problems early.

There are a number of randomised controlled trials (RCT) on the effectiveness of perioperative nutritional support in patients with gastrointestinal cancers but most are from one study centre and this has been taken into account when grading the recommendations.

Preoperative nutritional support can lead to decreased incidence of postoperative complications and length of hospital stay.²¹⁵⁻²¹⁹ A number of these studies targeted nutritional support to patients who were identified as being at high nutritional risk. | 1++

Early postoperative nutritional support is well tolerated and results in improved wound healing, decreased postoperative complications and shorter hospital stay.²¹⁵⁻²²³ | 1++

The literature on perioperative nutritional intervention suggests that both preoperative and postoperative nutritional support should be delivered predominately by the enteral (EN) route in preference to the parenteral (PN) route.^{220,221,224,225} | 1++

All patients with oesophageal or gastric cancer should be screened using a validated nutritional screening tool to assess nutritional risk. Those at risk of nutritional problems should have access to a state registered dietitian to provide appropriate advice.

B Patients undergoing surgery for oesophageal or gastric cancer who are identified as being at high nutritional risk should be considered for preoperative nutritional support.

B All patients undergoing surgery for oesophageal or gastric cancer should be considered for early postoperative nutritional support preferably by the enteral route.

7.8 ENDOSCOPIC TREATMENTS WITH CURATIVE INTENT

Endoscopic treatments offer an alternative to surgery for the management of HGD and early invasive cancer in the oesophagus or stomach. Non-surgical treatments have the advantage of low morbidity and mortality with preservation of normal digestion and quality of life. Cancer-free survival after endoscopic treatment is equivalent to that achieved by surgical resection in results from expert centres.^{226,227} | 2+

7.8.1 HIGH GRADE DYSPLASIA

HGD is most frequently detected in association with Barrett's oesophagus in patients taking part in surveillance programmes. HGD of the squamous oesophagus and the stomach can also be detected by endoscopy and biopsy, usually as an incidental finding.

Following diagnosis the absence of invasive disease should be confirmed. On average 45% of patients with a preoperative diagnosis of Barrett's HGD are subsequently found to have invasive cancer in the resected specimen.³⁸ This figure is based on case series reported prior to 1997. Subsequent improvements in assessment including thorough biopsy protocols, EUS and staging endoscopic mucosal resection (EMR) have contributed to a lower rate of missed adenocarcinoma.²²⁸ In this study of 75 HGD patients without cancer, only 16% developed cancer during a follow up surveillance period of 7.3 years.

2+

The natural history of HGD in an individual patient is difficult to predict and it may be helpful to distinguish between prevalent disease at the time of diagnosis and incident disease detected during surveillance.^{43,228,229} Prevalent HGD in the context of Barrett's oesophagus is frequently associated with invasive cancer particularly when macroscopic endoscopic abnormality is present (stricture, ulceration, nodularity) or when, histologically, the HGD is diffuse and associated with full thickness ulceration. Incident HGD detected during endoscopic surveillance is unlikely to be associated with invasive cancer particularly when macroscopic endoscopic abnormality is absent and histologically the HGD is focal and without ulceration.²³⁰⁻²³²

3

Accurate staging investigations and endoscopic biopsy mapping of the extent of the HGD are essential to determine whether invasive cancer is present before recommending treatment.²²⁹ All patients should undergo CT and EUS examination.²³³ Consideration should be given to EMR as a staging technique.²³⁴

2+

Endoscopic treatments for HGD in the absence of invasive cancer are curative and avoid the level of morbidity or mortality associated with surgical resection.²³³⁻²³⁶ It may be more appropriate to consider oesophagectomy in patients fit for surgery who have a long segment of Barrett's oesophagus with widespread high grade dysplasia in the absence of a focal lesion.

2+
4

The range of endoscopic treatments includes EMR, photodynamic therapy (PDT), laser therapy, and argon plasma coagulation (APC). There is no evidence that one endoscopic treatment is superior to another in the oesophagus. EMR offers the advantage of providing additional staging information.²³⁴ This may be important in the otherwise fit patient as pathological evidence of submucosal invasion is an indication to consider oesophagectomy.²²⁷ Gastric HGD lesions are best treated with EMR as these are usually detected by biopsy of a macroscopic abnormality and treatments such as PDT cannot target the lesion accurately. Multiple different treatment options are often necessary in an individual patient. Treatment choice should not be dictated by local facilities.²³⁴

2+

B Patients diagnosed with high grade dysplasia should have careful assessment (CT, EUS, rigorous biopsy protocol +/- EMR) to exclude coexisting cancer.

B In the absence of invasive cancer, patients with high grade dysplasia should be offered endoscopic treatment.

C The assessment and management of patients with high grade dysplasia should be centralised to units with the appropriate endoscopic facilities and expertise.

7.8.2 EARLY CANCER

A variety of endoscopic treatments are available for curative treatment in patients with superficial oesophageal cancer or early gastric cancer. In a Cochrane review of EMR for early gastric cancer no randomised controlled trials comparing EMR with surgery were identified.²³⁷ Five year survival rates after endoscopic treatment of patients with early gastric cancer or superficial squamous oesophageal cancer are between 80 and 95%, similar to survival after resection.^{226,227,238,239} Long term follow up for endoscopic treatment of superficial oesophageal squamous cancer has not been reported in Western populations. Three year survival of 88% has been reported in the context of Barrett’s adenocarcinoma.²³³

2+
3

Tumours should be accurately staged before considering any alternatives to surgery. EMR may be considered to be a staging investigation as the histological examination of the specimen provides definitive information about depth of tumour invasion.²³³

2++

Endoscopic treatments can only be curative if there is no appreciable risk of lymph node metastases being present at the time of treatment. In the stomach the following criteria reliably predict absence of lymph node metastasis:

- lesion < 2 cm in size
- well or moderately differentiated histology
- no macroscopic ulceration
- invasive disease limited to mucosa and certainly no deeper than the superficial submucosa
- no residual invasive disease after EMR.

2+

When these criteria are met lymph node metastases exist in only 0- 4% of patients.²²⁶

Although developed for patients with early gastric cancer most of these criteria can also be used to predict the absence of lymph node metastases in patients with superficial squamous oesophageal cancer and Barrett’s adenocarcinoma. In these cancers superficial submucosal invasion is associated with lymph node metastases in approximately 25% of cases.²²⁷ Using these criteria to select patients, the five-year disease-free survival after endoscopic treatment is at least equivalent to surgical resection.^{227,233,234,238,239}

2+

The main complications of EMR are bleeding and perforation. Risk of major complications can be less than 1%.^{234,238,239} Following removal, detailed pathology of the resected lesion should be carried out. When the submucosa is involved surgical resection should be considered if the patient is fit.²²⁷

3

Following treatment of the invasive component with EMR, additional endoscopic treatment for residual HGD in the surrounding mucosa may be necessary. Complementary techniques such as PDT, laser or APC may also be useful.^{233-236,240} Patients should remain in endoscopic surveillance programmes due to the high risk of developing additional tumours in the future, estimated to be about 30%.^{226,233}

3

B Superficial oesophageal cancer limited to the mucosa and early gastric cancer limited to the superficial submucosa should be treated by EMR.

D Mucosal ablative techniques such as PDT, APC or laser should be reserved for the management of residual disease after EMR and not for initial management if invasive disease is present in patients fit for surgery.

Patients should be informed of the risks and benefits of endoscopic treatments as an alternative to surgical resection in order to allow them to make an informed decision regarding choice of procedure.

The assessment and management of patients with early oesophageal or gastric cancer should be centralised to units with the appropriate endoscopic facilities and expertise.

8 Neoadjuvant and adjuvant therapies

Many of the studies appraised for this section are limited by their lack of standardisation of quality and radicality of surgery (see section 7). This has been taken into consideration when making recommendations.

- ☑ Chemotherapy and radiotherapy should be prescribed, dispensed, administered and supervised in a safe and effective manner in accordance with the Joint Collegiate Council for Oncology Guidelines,²⁴¹ clinical oncology good practice guidelines²⁴² and Scottish Executive advice.^{243,244}

8.1 OESOPHAGEAL CANCER

8.1.1 NEOADJUVANT (PREOPERATIVE) THERAPIES

Chemotherapy in patients with oesophageal cancer

A Cochrane meta-analysis of 11 randomised trials involving 2,051 patients found that preoperative chemotherapy plus surgery offers a survival advantage at five years compared to surgery alone for resectable thoracic oesophageal cancer of any histological type. The number needed to treat (NNT) for one extra survivor at five years was 11 patients.²⁴⁵ The conclusions of this review are at variance with previous systematic reviews. This may relate to the clinical heterogeneity among the included trials.^{246,247} The two largest RCTs in the current Cochrane meta-analysis produced the most discordant results. The MRC OEO2 study found that two preoperative cycles of cisplatin and 5-fluorouracil improved survival (median 16.8 months versus 13.3 months; $p=0.04$),²⁴⁸ whilst the second study, using the same agents at higher dose, with additional postoperative dosing failed to show a survival advantage.²⁴⁹ Sensitivity analysis shows that overall the results consistently demonstrate no survival advantage for preoperative chemotherapy until the fifth year following randomisation. The results are tempered by the increased toxicity and mortality associated with chemotherapy. The most beneficial chemotherapy combination appears to be cisplatin and 5-fluorouracil based although the dosing is unclear.

1+

- B** Patients with operable oesophageal cancer, who are treated surgically, should be considered for two cycles of preoperative chemotherapy with cisplatin and 5-fluorouracil or offered entry into a clinical trial.

Chemoradiotherapy in patients with oesophageal cancer

In a meta-analysis of randomised trials of neoadjuvant chemoradiation and surgery versus surgery alone in patients with oesophageal cancer, survival of the two patient groups was similar at one and two years, but three year survival in the neoadjuvant chemoradiation and surgery group was superior to that seen with surgery alone.²⁵⁰ Only one of the trials in the meta-analysis reported a statistically significant overall increase in three year survival with preoperative chemoradiation.²⁵¹ This study was criticised for a lack of preoperative CT staging, premature closure, and poor survival in the surgery alone arm. Two other trials showed no survival advantage at five years. Significant concerns remain about increased postoperative mortality.²⁵⁰

1+

- B** Preoperative chemoradiotherapy for patients with oesophageal cancer is not recommended outside clinical trials.

Radiotherapy in patients with oesophageal cancer

A meta-analysis has shown no significant improvement in survival from preoperative radiotherapy in patients with oesophageal cancer.²⁵²

1+

- A** Preoperative radiotherapy is not recommended for patients with oesophageal cancer

8.1.2 ADJUVANT (POSTOPERATIVE) THERAPIES

Chemotherapy in patients with oesophageal cancer

A review reporting two RCTs found no survival benefit associated with the use of postoperative chemotherapy in patients with oesophageal cancer.²⁵³

1+

A Postoperative adjuvant chemotherapy is not recommended for patients with oesophageal cancer

Chemoradiotherapy in patients with oesophageal cancer

No data were identified to support the use of postoperative combined chemoradiotherapy for oesophageal cancer.

Postoperative adjuvant chemoradiotherapy is not recommended for patients with oesophageal cancer.

Radiotherapy in patients with oesophageal cancer

Postoperative radiotherapy can reduce local recurrence rates in patients with oesophageal cancer, but has not shown a survival benefit.²⁶⁷ It may be appropriate to consider such treatment for those patients with a high risk of local recurrence (involved circumferential margin), but low risk of early distant relapse (no or low numbers of involved lymph nodes). There is currently insufficient evidence on which to base a recommendation.

3

8.2 GASTRIC CANCER

8.2.1 NEOADJUVANT (PREOPERATIVE) TREATMENT

For patients with gastric cancer, meta-analyses and RCTs show no survival benefit for neoadjuvant chemotherapy or radiotherapy compared to surgery alone.^{254,255}

1+

A The neoadjuvant use of either chemotherapy or radiotherapy for patients with gastric cancer is not recommended outside clinical trials.

8.2.2 ADJUVANT (POSTOPERATIVE) THERAPIES

Chemotherapy in patients with gastric cancer

Meta-analyses of postoperative chemotherapy in patients with gastric cancer have suggested a small survival advantage, particularly if lymph nodes are positive. Toxicity can be significant, and the optimum treatment regimen has not yet been defined.^{254,255}

1+

B Postoperative chemotherapy for patients with gastric cancer is not recommended outside a clinical trial.

In one small randomised study, adjuvant hyperthermic intraperitoneal chemotherapy decreased recurrence rates from gastric cancer and improved survival in comparison to controls, with a five year survival rate of 61% compared to 42% following surgery alone. This approach remains investigational.²⁵⁶ Studies of adjuvant immunotherapy have produced conflicting results.²⁵⁵

1+

C Intraperitoneal chemotherapy and immunotherapy for patients with gastric cancer are not recommended outside a clinical trial.

Chemoradiotherapy in patients with gastric cancer

An RCT of 556 patients with resected adenocarcinoma of the stomach or oesophagogastric junction showed a survival advantage with postoperative chemoradiation compared to surgery alone.²⁵⁷ Concerns have been expressed about the quality and lack of uniformity of the surgical approach in this study, as well as levels of treatment related toxicity.

1

Postoperative chemoradiation for patients with gastric cancer is not recommended outside a clinical trial.

8.3 PERIOPERATIVE CHEMOTHERAPY

The use of the standard regimen for advanced gastric and oesophageal cancer, epirubicin, cisplatin and continuous 5-fluorouracil (ECF) in the perioperative setting has been investigated in a randomised trial of perioperative chemotherapy and surgery versus surgery alone for resectable gastric and lower oesophageal tumours (the MRC Adjuvant Gastric Infusional Chemotherapy; MAGIC trial). The chemotherapy comprised three pre- and three postoperative cycles of ECF. Overall survival was significantly better in the surgery plus chemotherapy group (hazard ratio 0.75; 95% Confidence Interval; CI 0.60 – 0.93; $p = 0.009$) corresponding to five-year survivals of 36% (surgery plus chemotherapy) and 23% (surgery alone). The progression free survival was also significantly better in the chemotherapy plus surgery group (hazard ratio 0.66; 95% CI 0.53 – 0.81; $p < 0.0001$).²⁵⁸ Postoperative chemotherapy was not administered to 45% of the patients randomised to the chemotherapy plus surgery arm; 42% of patients completed all six cycles of chemotherapy and surgery. The study evaluated a perioperative treatment strategy, and it is not possible to attribute the favourable outcome to any particular component of therapy.

1+

8.4 DOWNSTAGING OESOPHAGEAL AND GASTRIC CANCER

The possibility of downstaging advanced oesophageal and gastric cancers to render them operable has been investigated. In a study of ECF or MCF (epirubicin is substituted by mitomycin C) chemotherapy for patients with locally advanced or metastatic oesophageal or gastric cancer, 24 (10%) of the 233 patients with locally advanced disease proceeded to potentially curative resection following a good response to chemotherapy. The survival of this subset was not separately reported, but 10 of these 24 patients survived more than two years.²⁵⁹

1+

In patients with gastric cancer there is weak evidence that R0 resection rates and survival following chemotherapy are increased compared to historical controls.²⁶⁰

4

D Patients with locally advanced disease having chemotherapy/chemoradiotherapy should have their response assessed for an impact on the potential to operate; following a good response the patient should be restaged and the role of surgery re-evaluated by the multidisciplinary team.

9 Non-surgical treatments with curative intent

9.1 CHEMORADIOTHERAPY

External beam radiation either alone or combined with chemotherapy can be used in the radical non-surgical treatment of oesophageal cancer, but has no established role in the definitive treatment of gastric cancer.

In a meta-analysis, concomitant combined chemoradiation was superior to radiation alone in patients with inoperable non-metastatic squamous cancer of the oesophagus.²⁶¹ Limitations of the analysis include lack of definition of the criteria for non-operability and staging without the benefit of all currently available modalities. In a randomised study, a five-year survival of 26% (95% CI 15-37%) was reported, superior to radiotherapy alone.²⁶²

1+

There are limited RCT data on the role of combined chemoradiation in patients with operable squamous cancer, operable adenocarcinoma or locally advanced adenocarcinoma of the oesophagus. For patients with locally advanced disease or operable oesophageal cancer who decline surgery or who are unfit for surgery, chemoradiation may be an appropriate alternative.²⁶²

The Royal College of Radiologists have made recommendations on radiotherapy dose and fractionation in this setting.²⁶³

4

C Chemoradiotherapy should be considered in patients with oesophageal cancer who have locally advanced disease, those unfit for surgery or those who decline surgery.

9.2 RADIOTHERAPY

External-beam radiotherapy may be used as a single modality curative (radical) treatment for oesophageal cancer.⁹⁸ Meaningful comparison between surgery and radical radiation therapy for the primary treatment of resectable oesophageal cancer is restricted by the lack of comparative clinical trials in otherwise fit patients with (resectable) oesophageal cancer.

4

Retrospective series indicate that patients selected for radical treatment with radiotherapy have similar results overall to patients undergoing surgery. The mortality associated with radical radiotherapy is small and the morbidity significantly lower than that following surgery.²⁶⁴⁻²⁶⁶ Radiotherapy can achieve relief of dysphagia and local control of the disease but remote failure is common.²⁶⁷ A randomised trial of 99 patients comparing surgery with radiotherapy in patients with operable oesophageal cancer found that survival and improvement in swallowing was better in the surgery arm.²⁶⁸ There were a number of methodological deficiencies with this trial and its analysis which suggest caution in the interpretation of its results. Contraindications to radical radiotherapy include long tumour length and/or the presence of a tracheo- or broncho-oesophageal fistula.^{265,266}

3

4

1-

A variety of radiation therapy regimens have been described (40 to 70 Gy in 20 to 30 fractions) but no difference in survival benefit was detected between them.²⁶³ The Royal College of Radiologists have made recommendations on radiotherapy dose and fractionation.²⁶³

4

The main disadvantage of radical radiotherapy is the development of a fibrous stricture in 44% of patients treated.²⁶⁹ Accelerated fractionation regimens that decrease the overall time of treatment may enhance local control at the expense of increased stricture rate.²⁷⁰

3

Brachytherapy (intracavity irradiation) with caesium or iridium pellets loaded into an applicator and placed in the lumen of the oesophagus is another technique for delivering radiotherapy locally. Its main limitation is the limited effective treatment distance. The technique is useful for palliation of dysphagia but not for radical treatment unless combined with external-beam radiotherapy.⁹⁸

4

D In patients with oesophageal cancer who are not suitable for surgery and intolerant to chemoradiotherapy, single modality radiotherapy can be used as a curative treatment in localised disease.

Single modality radiotherapy has no established role in the definitive treatment of gastric cancer.²⁷¹

9.3 CHEMOTHERAPY

No evidence was identified to suggest that chemotherapy as a single modality has any role in the curative treatment of oesophageal or gastric cancer.

10 Palliative care

10.1 CHANGING PRIORITIES: QUALITY OF LIFE, COMORBIDITY AND PERFORMANCE STATUS

Fifty to eighty per cent of patients with oesophageal cancer and 30 to 50% of patients with gastric cancer have inoperable disease at diagnosis.²⁷²⁻²⁷⁷ Studies of palliative treatments in patients with oesophageal and gastric cancers have focused on control of dysphagia and improvements in survival. Some have used surrogate markers of quality of life such as number of hospital free days. It is increasingly recognised that quality of life (QoL) improvements are more important to many patients and carers than short term survival benefits.²⁷⁸⁻²⁸¹ Acknowledging this, clinical services may need to change to provide improved communication, patient access and short term inpatient admissions for symptom control.^{282,283}

Quality of life can be measured objectively in cancer patients^{284,285} and in oesophageal cancer patients specifically.²⁸⁶ Only a few studies were identified which make use of validated quality of life tools in patients with oesophageal cancer.^{287,288} Quality of life assessments are more sensitive to change with palliative interventions than are gastrointestinal symptoms alone, such as dysphagia.²⁷⁸ Caution is necessary in employing QoL assessment as the different questionnaires, although validated and encompassing all the major parameters, have different emphases. The European Organisation for Research and Treatment of Cancer (EORTC) questionnaire focuses on somatic symptoms and functional capabilities whereas Functional Assessment of Cancer Therapy (FACT) concentrates on global quality of life and Short Form SF36 on psychological well-being.²⁸⁰

2⁺⁺

Comorbidity and performance status influence treatment selection, curability and treatment outcomes.^{289,290} There is evidence that patients with poor performance status gain little from invasive palliative interventions.^{291,292}

2⁺
2⁻

There is little published information on the extent to which comorbidity and performance status influence decision making and outcomes of interventions.

C Studies of palliative treatments in patients with oesophageal or gastric cancer should use validated questionnaires to measure quality of life outcomes and should include comorbidity and performance status.

Integration of quality of life assessment into routine clinical practice should be encouraged. This may aid appropriate treatment selection and enhance audit of treatment outcomes.

10.2 SUPPORTIVE AND PALLIATIVE CARE

The scope of care goes beyond symptom control to encompass a more holistic approach. Supportive care is an umbrella term for all services, generalist and specialist, that may be required to support patients with cancer and their carers. It is given equal priority alongside diagnosis and treatment.²⁹³ It includes palliative care which is defined as the active holistic care of patients with advanced progressive illness. Management of pain and other distressing symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.²⁹⁴ A Cochrane review of "best supportive care", a term often used in the control arm of oncology trials, found the term to be poorly and variably defined and suggested that improvements in methods of measuring supportive care will allow QoL measurements to be made against different levels and types of care.²⁹⁵

4

D Studies of supportive care should clearly define interventions and use validated quality of life end points.

10.3 ROLE OF PALLIATIVE CARE TEAMS

In the general population of patients with cancer, intervention of a specialist palliative care team improves symptom control, reduces hospital readmissions and increases the likelihood of patients dying in a place of their choosing.²⁹⁶⁻²⁹⁹ No evidence was identified relating specifically to patients with oesophageal or gastric cancer.

2+
3

C Patients with oesophageal or gastric cancer should have access to a specialist palliative care team.

NHS Quality Improvement Scotland (NHS QIS) has set standards for both basic palliative care skills and provision of specialist palliative care services.³⁰⁰

10.4 INVASIVE PALLIATIVE TREATMENTS

If outcomes are to be improved, careful selection for invasive therapy is essential (see section 10.1). The acute hospital multidisciplinary team is ideally placed to achieve this and should integrate with the palliative care team to provide ongoing symptom control and holistic support for patients and their carers from the point of presentation with advanced disease.

Selection of patients for invasive palliative interventions should be carried out by a multidisciplinary team. There should be integration of the acute multidisciplinary team and the palliative care team to ensure appropriate continuous palliative care.

In the palliation of malignant dysphagia the use of endoscopic ablative therapy, stenting, radiotherapy or brachytherapy is complementary rather than mutually exclusive.^{98,301} There is significant variation in the delivery of palliative therapy throughout Scotland both in terms of the number of patients actually treated, the type of intervention and in terms of the outcome.³⁰²

3

Endoscopic ablative therapies, stenting, external beam radiotherapy and brachytherapy should be used as complementary techniques.

10.5 ENDOSCOPIC ABLATIVE THERAPIES

For patients with exophytic tumours, laser therapy has superseded radiotherapy, bypass or early tube techniques for control of obstructive oesophageal symptoms and is associated with lower mortality and improved quality of life.⁹⁸ Laser ablation produces better symptom palliation than ethanol injection.³⁰³

4
2++

Addition of brachytherapy or external beam radiotherapy to laser therapy prolongs the interval between treatments, but is associated with an increased incidence of strictures and fistulas.³⁰⁴⁻³⁰⁶

1+

Nd-YAG (neodymium-yttrium aluminium garnet) laser therapy improves quality of life more than uncovered and selected covered stenting, with lower procedure related mortality and longer survival.²⁸⁷ Re-interventions are frequent (every six weeks) and secondary treatments are required in up to 30% of cases.

1+

Photodynamic therapy improves dietary intake, performance status, dysphagia grade and duration of response compared with Nd-YAG laser therapy.³⁰⁷ There are more frequent, but "minor" side effects (photo-sensitisation) from PDT contrasting with less frequent, but major side effects (perforations) for laser therapy.³⁰⁸

1+

Both laser and PDT tumour ablations are effective near the upper oesophageal sphincter where stents are contraindicated.^{272,287,308}

3

Lasers and PDT can also be used effectively to treat tumour overgrowth after stenting.^{292,309}

3

B Laser or photodynamic therapy should be used for initial control of obstructive symptoms caused by exophytic tumours in the oesophagus including tumours near the upper oesophageal sphincter.

D Laser or photodynamic therapy should be considered for control of tumour overgrowth in stented patients.

Case series describing the use of argon plasma coagulation for palliation of obstructive oesophageal symptoms suggest that it may compare functionally with PDT and laser ablative therapy.³¹⁰⁻³¹² No direct comparisons have been made. APC may be useful for tumour overgrowth around metal stents as, unlike laser, it does not fracture the metal.³¹³

3

10.6 STENTING

Stents are available for the oesophagus and for the gastric outlet. Stent design is a rapidly evolving area. A summary of the properties and usage of stents available in the UK has been published by the British Society of Interventional Radiology.³¹⁴

4

10.6.1 OESOPHAGUS

In a case series of patients with oesophageal cancer (n = 100) symptom palliation was achieved in 91% of patients by the insertion of Atkinson prostheses. There was a high 30-day mortality (32.6%) and significant procedure related morbidity (23% during initial admission, of which 11% were perforations; 20% subsequent to initial admission).³¹⁵

3

Self expanding metal stents are associated with lower mortality, reduced length of hospital stay and improved quality of life when compared with plastic prostheses.^{81,316} Early uncovered metal stents produced more improvement in dysphagia with fewer complications and fewer re-interventions than early covered stents.³¹⁷ Partially covered metal stents achieve the best symptom control available with tubes: improvement in dysphagia with low mortality and rate of migration and fewer complications due to tumour ingrowth than uncovered metal stents.³¹⁸

1+
1++

In an underpowered RCT, no significant differences were detected between different types of covered stents.³¹⁹ Later covered stents show lower migration rates (5%) than earlier designs.³²⁰

1-
1+

Metal stents may produce chest pain in two thirds of patients and reflux in one third. In addition, these stents may deteriorate with time.³²¹

2-

Reflux may be significantly reduced by the use of stents with an anti-reflux valve, although there may be increased risk of food bolus obstruction and migration.³²²⁻³²⁴

3

Self expanding plastic stents (SEPS) have similar functional results to self expanding metal stents (SEMS), with less postprocedural chest pain.³²⁵ No studies have directly compared SEPS and SEMS.

3

Increasing numbers of new stents have been designed to be removable.³¹⁴ Removable stents may be used in association with other complementary techniques in selected patients.

4

Covered stents are effective in the palliation of symptoms from oesophagorespiratory fistulae with fistula occlusion rates of 77-92%.^{326,327}

2-

Stents are effective in the palliation of recurrent symptoms after failure of primary therapy (resection, radiation or chemoradiation). Initial concerns about fatal complications have not been substantiated in subsequent work.^{328,329}

2-

An RCT comparing stenting with brachytherapy has shown brachytherapy to be superior if patients live longer than 140 days. Stenting produced more rapid and better improvement in dysphagia over the first 30 days.²⁸⁸ Patient selection for these interventions is critical for the best patient outcomes.

1+

B Partially covered self expanding metal stents are the intubation of choice for patients with obstructive oesophageal symptoms.

C Partially covered self expanding metal stents should be used to control obstructive oesophageal symptoms either following or instead of laser therapy, depending on the availability of local expertise.

The palliative management of patients with mild dysphagia is discussed in section 10.9.2.

10.6.2 GASTRIC OUTLET

Initial experience in phase 1 and phase 2 trials has shown high technical success rates for self expanding metal stents in palliation of malignant gastric outlet obstruction (97-100%) with minimal mortality and 17% morbidity. Seven to twenty two per cent of patients in these studies required re-interventions with further stents. Quality of life end points were restricted to improvements in dietary intake.³³⁰⁻³³³ 2+
2-

Compared with open surgical bypass, patients having enteral stents have reduced hospital stay (4 days versus 14 days, 40% may be placed as a day case) and similar survival.³³⁴ 2+

10.7 DILATATION

Oesophageal dilatation alone provides only transient symptom improvement and there is no good quality evidence comparing its use with other modalities.⁹⁸ 4

D The use of oesophageal dilatation alone should be avoided.

10.8 PALLIATIVE SURGERY

The evidence in relation to surgery as a palliative intervention is poor. There are no RCTs, and most observational studies are retrospective and take little account of comorbidity, performance status, likely survival and quality of life.

10.8.1 PALLIATIVE RESECTION OF THE OESOPHAGUS

In a case series, transthoracic oesophagectomy was superior to palliative radiotherapy, but no comparisons were available with ablative or stenting interventions.³³⁵ Mortality in selected cases can be held under 10% but is often nearer 20%. Morbidity remains high (26-37%).^{151,273,335} 3

Morbidity (anastomotic leakage; respiratory complications; vocal cord paralysis) may be reduced by performing anastomoses in the thorax rather than in the neck.³³⁶ 2-

Where quality of life assessment is made, the worst outcomes are noted in patients subjected to thoracotomy, who are ultimately unresectable/incurable and live less than two years. Such patients have decreased QoL, increased morbidity and increased mortality relative either to groups resected and living more than two years or to groups treated without resection, but with other invasive palliative therapies.¹⁵¹ 2++

Transhiatal oesophagectomy may be an alternative to thoracotomy. No direct comparisons are available with transthoracic oesophagectomy or with more modern ablative or stenting techniques.^{337,338} 3

C Oesophagectomy (*transthoracic or transhiatal*) should not be performed with palliative intent in patients with oesophageal cancer.

10.8.2 PALLIATIVE BYPASS FOR OESOPHAGEAL CANCER

Substernal bypass is no longer used as a planned procedure for patients with oesophageal cancer, because of the associated high morbidity (77%), re-operation rates (27%), 30-day mortality (32%), and dismal survival (1.9 months).^{339,340} 3

D Substernal bypass for oesophageal cancer should not be performed with palliative intent.

10.8.3 PALLIATIVE RESECTION OF THE STOMACH

Palliative resection of the stomach has a similar (or lower) 30-day mortality compared to gastric bypass.^{274,275,277,341} There is also increased survival after palliative resection compared with no resection.³⁴² On multivariate analysis, factors which influence survival after palliative resection include:

- stage of disease - including degree of peritoneal dissemination^{276,343}
- tumour size - longer survival associated with tumours < 100 mm in diameter^{276,343}
- histological type - Lauren intestinal type better prognosis than diffuse type²⁷⁶
- degree of tumour differentiation- patients with well differentiated tumour survive longer²⁷⁶
- extent of lymphadenectomy - D2 resection confers no long term advantage over D0 or D1³⁴⁴
- addition of en-bloc resection or omentectomy – where limited dissemination^{345,346}
- gastric perforation - perforation of incurable gastric cancer carries significant initial mortality but subsequent survival is unaltered relative to the unperforated group.³⁴⁷

Evidence about the importance of age is conflicting.^{348,349}

Caution is necessary in interpreting these observational studies with no quality of life end points.

After palliative resection, the benefit of a new reconstruction involving colonic interposition within the seromuscular oesophagus has been incompletely assessed.³⁵⁰

C Palliative gastrectomy should be avoided in patients with gastric cancer who have disseminated peritoneal disease.

D D2 lymphadenectomy should be avoided in patients with gastric cancer in the palliative setting.

D Health professionals should take the following factors into account when considering palliative gastric resection:

- **peritoneal disease** (*favour minimal*)
- **tumour diameter** (*favour < 100 mm*)
- **histological type** (*favour Lauren intestinal type*)
- **degree of differentiation** (*favour moderate to good differentiation*).

10.8.4 PALLIATIVE GASTRIC BYPASS

Gastric bypass has a high mortality (33%) and studies of this intervention rarely assess quality of life with validated tools.^{351,352} A small case series (n = 27) described outcomes for two types of open surgical bypass; gastrojejunostomy and gastric exclusion.³⁵³

In a small RCT (n = 18), morbidity (haemorrhage) was more serious after open gastro-jejunostomy compared with gastric outlet stenting, sometimes requiring re-laparotomy. Time to oral intake was delayed and hospital stay increased (10 days versus 3.1 days).³⁵⁴

Laparoscopic gastrojejunostomy is technically feasible with substantially lower mortality than reported for open bypass.³⁵⁵ There is no evidence comparing this technique with open surgery or intubation.

Ability to tolerate solids after gastric bypass is reduced when malignant ascites or small bowel obstruction is also present.³⁵⁶

D Laparoscopic bypass or gastric outlet stenting are alternatives to palliative gastric bypass.

D Palliative gastric bypass should be avoided when malignant ascites or small bowel obstruction are present.

10.8.5 EXPLORATORY LAPAROTOMY

Exploratory laparotomy is associated with high inpatient mortality (31%).³⁵² Appropriate staging may minimise the need for laparotomy (see section 5).

3

D Exploratory laparotomy alone should be avoided.

10.9 PALLIATIVE CHEMOTHERAPY AND RADIOTHERAPY

Chemotherapy and radiotherapy should be prescribed, dispensed, administered and supervised in a safe and effective manner in accordance with the Joint Collegiate Council for Oncology Guidelines,²⁴¹ clinical oncology good practice guidelines²⁴² and Scottish Executive advice.^{243,244}

10.9.1 PALLIATIVE CHEMOTHERAPY

Palliative chemotherapy may be given with the intent of increasing survival, benefiting quality of life and improving tumour related symptoms including dysphagia.

There is evidence from a systematic review and meta-analysis of four small RCTs, of a survival benefit of a few months from palliative chemotherapy compared with active supportive care for patients with gastric cancer. There are more limited data indicating a quality of life benefit.^{98,254}

4

1+

There are no equivalent data for oesophageal tumours but studies including patients with oesophageal, gastric and oesophagogastric junction tumours show no significant difference between sites in terms of benefit and no evidence to support a different treatment approach by site.⁹⁸

There are few randomised data using current regimens on squamous cancer of the oesophagus. Data from studies that include patients with squamous cancer do not suggest the need for a different treatment approach.⁹⁸

ECF is superior to 5-fluorouracil, doxorubicin and methotrexate (FAMTx) which is superior to 5-FU, adriamycin, mitomycin-C (FAM).^{98,254} ECF and MCF are equivalent in terms of response rates and survival and there is a suggestion that ECF is superior in terms of QoL, but the data are limited as patients progress and become unable to complete QoL forms. Such regimens can lead to an improvement in symptoms such as pain, nausea, vomiting and dysphagia in 70 - 80% of patients.²⁵⁹ Further data are required on the extent and duration of symptom improvement. Objective response rates are in the order of 40 - 45%.²⁵⁹

1+

The role of capecitabine in place of infusional fluorouracil (5-FU) in combination regimens awaits the outcome of large ongoing RCTs. The role of newer agents such as oxaliplatin, taxanes and irinotecan remains under investigation. There is no established role for routine use of second line chemotherapy.

B In patients with locally advanced or metastatic cancer of the oesophagus or stomach with good performance status combination chemotherapy including cisplatin and infusional 5-FU (such as ECF or MCF) should be considered.

Patients should have the opportunity to discuss the role of palliative combination chemotherapy with an oncologist and should be made aware of the modest survival benefit and potential symptomatic improvement, but potential toxicities, prior to a treatment decision.

10.9.2 EXTERNAL-BEAM RADIOTHERAPY

External-beam radiotherapy can improve dysphagia in 50-85% of patients with oesophageal cancer and may also palliate pain. Benefit appears more likely in patients with milder dysphagia managing a semi-solid diet or better. The time to improvement in swallowing is measured in weeks.⁹⁸ There is no evidence from RCTs to allow a firm recommendation about radiotherapy dose and fractionation. Expert opinion suggests that doses in the range of 20 Gy in five daily fractions and 30 Gy in ten daily fractions are acceptable.²⁶³

4

There are no RCT data comparing external-beam radiotherapy with brachytherapy or external-beam radiotherapy with stenting.

D Palliative external-beam radiotherapy is an appropriate option for the treatment of mild dysphagia in patients with oesophageal cancer.

Tumour bleeding from both the stomach and the oesophagus may benefit from external beam radiotherapy. Although this technique forms a limited part of current practice no good quality data on its effectiveness have been identified.

External-beam radiotherapy has an important role in the symptomatic treatment of bone pain from metastatic disease, as well as brain metastases. Examining studies in this area was outside the scope of this guideline.

10.9.3 PALLIATIVE CHEMORADIOTHERAPY

No evidence has been identified to support combined chemoradiation in the palliative setting for either oesophageal or gastric cancer. For some patients it will be appropriate to consider the use of both radiotherapy and chemotherapy during the course of their illness.

10.9.4 BRACHYTHERAPY

Endoluminal brachytherapy can palliate dysphagia in over 50% of patients with oesophageal cancer. There is evidence that 16 Gy given in two weekly treatments and 18 Gy given in three weekly treatments are equivalent and superior to 12 Gy in two weekly treatments.^{357,358}

3

There are no RCT data comparing either to the commonly used 15Gy in a single treatment. No recommendation can be given about the optimal dose and fractionation of oesophageal brachytherapy.

In comparison with brachytherapy, stent placement provides more rapid improvement in dysphagia but long term relief of dysphagia was better after brachytherapy. In patients who lived longer than 140 days brachytherapy resulted in better dysphagia control, reduced complications and increased health related quality of life. There was a 30 day lag to onset of these benefits and stenting achieved better control in the shorter term.²⁸⁸

1++

D Endoluminal brachytherapy is an option for patients with dysphagia from oesophageal cancer.

10.10 CONTROL OF OTHER SYMPTOMS

Patients with oesophageal or gastric cancer experience a range of symptoms including pain, anorexia, cachexia, nausea/vomiting, anaemia and bleeding. Evidence specific to control of such symptoms in these cancers is limited.

It is beyond the scope of this guideline to deal with generic symptom control in cancer patients. Palliative care guidelines are in place and can be accessed via; www.palliativecarescotland.org.uk/links/index.htm or www.palliativecareglasgow.info/pages/guidelines.asp

Any patient at any stage of their cancer journey who has symptomatic or supportive care needs which are difficult to address should have ready access to a specialist palliative care team.

10.10.1 PAIN

The World Health Organisation (WHO) analgesic ladder sets out generic recommendations on cancer pain relief.³⁵⁹ There is no specific evidence relating to pain control in patients with oesophageal or gastric cancer. For a more detailed discussion of pain assessment and management see the SIGN guideline on control of pain in patients with cancer.³⁶⁰

4

Coeliac axis plexus block (CPB) is an effective method for relieving pain associated with pancreatic and non-pancreatic intra-abdominal malignancies. One meta-analysis examined pain relief after CPB in 1,145 patients; 410 of these had non-pancreatic cancers. Partial to complete pain relief occurred in 60-90% of patients irrespective of techniques used. There was no apparent difference in pain relief in pancreatic compared to non-pancreatic cancers. Descriptions of pain quality, site, intensity, or duration were limited and no quality of life information was included but a reduction in opioid requirement may be possible. Adverse effects were common but transient; severe adverse effects were uncommon (2%).³⁶¹

1+

D The principles of treatment outlined in the World Health Organisation pain relief programme should be followed (*WHO analgesic ladder*).

C Coeliac axis plexus block should be considered in patients with severe upper abdominal pain who are intolerant of, or have pain unresponsive to, other analgesic measures.

10.10.2 ANOREXIA AND CACHEXIA

Assessment and treatment of any reversible cause of anorexia and cachexia eg pain, anxiety, nausea or oral problems is essential.

Corticosteroids and megestrol acetate can increase appetite in patients with cancer.³⁶²⁻³⁶⁴ Weight may be increased with a combination of megestrol acetate and ibuprofen in patients with colorectal cancer, and eicosapentanoic acid (EPA) in patients with pancreatic cancer.^{365,366} The effects of these drugs in patients with oesophageal or gastric cancer are unknown.

3

D Corticosteroids or megestrol acetate should be considered for patients with advanced oesophageal or gastric cancer who are anorexic.

10.10.3 NAUSEA AND VOMITING

Assessment and treatment of any reversible cause eg infection, drug interactions or biochemical abnormalities should be the first step. Generic guidelines in palliative care should be referred to.

In patients who develop bowel obstruction, octreotide may lessen the symptoms of nausea and vomiting and may be an alternative to intravenous fluids and nasogastric tube placement.^{367,368}

1+

A systematic review investigating the use of corticosteroids in the resolution of symptoms of malignant bowel obstruction has shown a non-statistically significant trend towards improvement.³⁶⁹ Short term side effects of this treatment are few and the use of corticosteroids can have beneficial effects on other symptoms, such as anorexia and weakness.^{370,371}

1+

2+

D Octreotide and corticosteroids should be considered to relieve symptoms of bowel obstruction caused by malignancy where interventional therapy is not possible or appropriate.

10.10.4 ANAEMIA

Anaemia is a common finding in patients with GI malignancies. This may be treatment related, a consequence of blood loss, or anaemia of chronic disease. Anaemia produces a range of symptoms, the principal one being fatigue.³⁷² Blood transfusion works quickly to improve symptoms of weakness and breathlessness and improves well-being in anaemic patients with cancer.^{373,374} The use of erythropoietin (EPO) can achieve similar symptomatic improvements but takes time for effect and the evidence that it diminishes transfusion requirements is conflicting.³⁷⁵ The EORTC have drawn up guidelines on the use of EPO based on evidence predominantly relating to chemotherapy induced anaemia.³⁷⁶ There is no specific reference to patients with oesophageal or gastric cancer.

2+
2-
3

- C Blood transfusion is recommended as the standard treatment for symptomatic anaemia.**
- D Erythropoietin use should be considered in accordance with agreed guidelines.**

10.10.5 BLEEDING

The prevalence of pre-treatment bleeding is rarely mentioned in studies of patients with oesophageal or gastric cancer. In a case series (n = 39), three patients with oesophageal cancer had pre-treatment bleeding.³²¹ No data on the prevalence of bleeding of gastric cancer at presentation has been found. Most studies are restricted to the incidence of bleeding following invasive palliation.

Fibrinolytic inhibitors (tranexamic acid and aminocaproic acid) have been used to control cancer-associated bleeding, but no oesophagogastric cases were included in this assessment.³⁷⁷

Oesophageal cancer

Bleeding after laser, PDT or APC therapy is rarely encountered.^{304,307,308,310} Bleeding after stenting is significantly more common with SEMS than with Atkinson prostheses or latex tubes and occurs in 10-16% of cases.^{272,287,318,319} Treatment has varied from blood transfusion to adrenaline injection, laser therapy, APC or external beam radiotherapy. The mortality associated with severe haemorrhage related to stenting is above 50%.^{287,319} The incidence of haemorrhage after brachytherapy is significantly less than after the use of self expanding metal stents.³⁵⁸ Haemorrhage after palliative oesophagectomy has not been reported.³³⁷

3

Gastric cancer

The incidence of haemorrhage is low (1-3%) following insertion of duodenal stents for gastric outlet obstruction.³³⁰⁻³³³

Gastrectomy can be effective in palliating bleeding gastric cancer.³⁴¹ Haemorrhage also occurs after palliative gastric resection (1-3%) and has a 50% mortality.^{274,275}

3

The incidence of haemorrhage after palliative gastric bypass has been reported at 55%³⁵³ but may be much lower (3%).^{274,275} Many patients were managed by transfusion only in these case series.

10.11 DIETETIC SUPPORT

As cancer stage advances, increasing weight loss occurs and this is associated with diminishing quality of life.³⁷⁸ Undernutrition in hospital patients, and factors which prevent a patient from eating adequately, are frequently not identified, and nutritional state declines throughout treatment. A screening and assessment process helps identify patients at risk of malnutrition.³⁷⁹

4

A systematic review highlighted the lack of evidence on the provision of dietary advice in the management of illness-related malnutrition.³⁸⁰ The review suggested that the provision of oral nutritional supplements may be more effective than dietary advice, or provide an additional benefit in enhancing short term weight gain, but whether this can be sustained, or whether survival and morbidity are also improved remained uncertain.

1+

An RCT of 309 patients (~25% with oesophageal/gastric cancer) compared spontaneous nutritional intake with nutritional intervention (which included home total parenteral nutrition; TPN). Results suggested beneficial effect on survival and energy balance in the treated group but no measure of quality of life was undertaken and the study was complicated by co-administration of anti-inflammatory agents and EPO.³⁸¹ 1+

Advice about individualised diet, food texture, food presentation and supplementation may improve nutritional behaviour or eating patterns in elderly patients with cancer (including oesophageal or gastric cancer) in the palliative setting.³⁸² Dietetic intervention can help address both patient and carer concerns and provides practical support to maximise oral intake and advise on the appropriateness of nutritional supplementation and artificial nutritional support.³⁸³ 2+
4

All patients with oesophageal or gastric cancer should be screened using a validated nutritional screening tool to assess nutritional risk. Those at risk of nutritional problems should have access to a state registered dietitian to provide appropriate advice.

Control of symptoms such as pain, nausea, constipation and depression and good mouth care should be considered, to enable patients to maintain an oral intake in a form appropriate to their condition and treatment.

10.11.1 ARTIFICIAL OR ASSISTED NUTRITION

Decisions about artificial or assisted nutrition require careful and sensitive discussion with patient, carer and multiprofessional team. Ethical guidelines are in place.^{384,385} 4

By improving the ability to tolerate fluids and diet, the effective use of endoscopic ablative therapies and intubation techniques may reduce the need for artificial or assisted nutrition. If a patient cannot sustain oral feeding, enteral tube feeding should be considered. Several methods are available: nasoenteric feeding (NEF); percutaneous endoscopic gastrostomy (PEG); radiological inserted gastrostomy (RIG); surgical gastrostomy and jejunostomy.

Enteral feeding in any form is physiologically more beneficial, has fewer complications and is cheaper than TPN.^{386,387} PEG and RIG tubes are less likely to be removed or dislodged than nasogastric tubes. They are cosmetically more acceptable and easier for patients and carers to use at home.³⁸⁸ PEG and RIG tube insertions are safe and effective alternatives to surgical gastrostomy.³⁸⁹ One retrospective series examined the risks of PEG-tube insertion in 229 patients with oesophageal cancer over a 10 year period.³⁹⁰ PEGs were successfully inserted in 97% of patients (with the aid of dilatation in 45%). Mortality in this series was 0.9%. Complications included serious infection around PEG tube site, serious leakage, and abdominal pain in the first 24-48 hours. Results from a series of 113 RIG tube insertions (mostly head and neck patients: only eight with oesophageal cancer) carried a mortality of 1.9% and a major morbidity of 7.8% (peritonitis and wound infections).³⁹¹ This compares favourably to surgical gastrostomy which carries a mortality risk of 3-16%.³⁹² 3
4

Symptoms of dehydration and poor nutritional intake are the usual indications for feeding tube insertion. There is a lack of good evidence to support nutritional benefit to oesophageal or gastric cancer patients in the palliative setting, and no evidence regarding quality of life or survival benefit.³⁹¹

The need for artificial nutrition should be discussed with the patient, carer and multiprofessional team. Symptomatic, ethical, prognostic and practical issues should all be considered.

11 Information for discussion with patients and carers

This section of the guideline presents the questions and concerns that patients may express at the different stages of their journey. It is based on a series of discussions between a small group of patient representatives. It is not exhaustive.

11.1 EFFECTIVE AND SENSITIVE COMMUNICATION

Health professionals should be aware of the profound emotional consequences associated with a diagnosis of cancer and the complexity of dealing with each patient in a holistic manner addressing their spiritual, emotional and psychological needs alongside medical concerns. Successful communication with patients and their carers depends on the appropriate and timely use of all relevant skills within the multidisciplinary team. This may include individuals from outwith the healthcare system such as former patients, representatives of support organisations and pastoral carers. There should be sensitive, early and ongoing communication between the multidisciplinary team (MDT) and the patient to ensure the patient is fully involved in all decisions and that their views and preferences are clearly understood by those involved in treatment planning. A named contact person from the MDT should be available to each patient and take responsibility for guiding the patient throughout the management pathway.

At all stages of information giving, in particular around the time of diagnosis, the following aspects of care should be given suitable consideration and, if appropriate, guided by agreed protocols in order that a positive approach to communication with patients may be implemented.

Empowering the patient - Would it be possible to empower the patient to control the discussion and take the lead in communications? This will involve giving time, providing encouragement and using silences to allow the patient to think. In some cases patients may feel obliged to seek detailed information whilst not expressing their sole immediate concern: 'will I survive this?'

Timing of information delivery – Is the information being delivered sensitive to the needs of the patient at that time? Unnecessary delays in informing patients of their diagnosis generate considerable anxiety in patients with suspected cancer.

Setting of information delivery - Is the physical setting appropriate (formal/ informal)? Are the right people present to support the patient and carer?

- Patients with oesophageal or gastric cancer should be offered written information at the time of diagnosis detailing the possible sequence of events and providing them with a named contact on the multidisciplinary team.

Detailed patient information leaflets can be downloaded from Core or from CancerBacup.

Oesophageal Cancer

www.corecharity.org.uk/Default.aspx?docname=doc_oesophcancer
www.cancerbacup.org.uk/Cancertype/Gulletoesophagus

Gastric Cancer

www.corecharity.org.uk/Default.aspx?docname=doc_stomachcancer
www.cancerbacup.org.uk/Cancertype/Stomach

11.2 AREAS OF CONCERN TO PATIENTS

The following sections suggest questions which may arise and information which may be desired by patients at three stages of their illness.

11.2.1 AT TIME OF DIAGNOSIS AND STAGING

- will I live?
- what can be done?
- who can I talk to?
- what is the staging process?
- what are the options available for treatment of my cancer?
- although an operation may be available to cure my cancer are there any alternatives?
- what are the advantages and disadvantages of each of the alternative options?
- although my cancer may be operable are there reasons why an operation is not felt to be the best way to treat the cancer?

11.2.2 AROUND THE TIME OF SURGERY

- what is involved in the surgery?
- how often is this operation carried out at this hospital?
- what are the risks involved?
- what happens immediately after surgery?
- how much pain will be involved?
- what immediate difficulties will I face?
- what are the long term prospects?
- what effect will this surgery have on my quality of life? (including eating/drinking, fatigue, sleeping, work/social activities)
- what about scarring?
- what follow up will there be?
- practical issues - care planning, financial security etc

11.2.3 POTENTIAL PHYSICAL PROBLEMS

Where appropriate, the possibility of experiencing the following physical problems should be outlined. It must be emphasised to patients that they will not experience all these symptoms.

- difficulties around eating and drinking (in particular the social difficulties associated with eating outside the home)
- difficulty with swallowing that may require an endoscopic dilatation
- dumping syndrome (nausea, weakness, sweating, palpitations occurring after ingestion of food)
- diarrhoea/constipation
- acid reflux
- vomiting
- weight loss
- problems sleeping comfortably
- fatigue
- reduced capacity for physical activity
- need for long term medication/dietary supplementation (iron, folate, vitamin B12, vaccination, antibiotic therapy).

11.2.4 ON COMMENCING PALLIATIVE TREATMENT

- what treatment do you recommend?
- why?
- which symptoms can it help?
- how will it help?
- what's involved?
- what are the side effects/ drawbacks/limitations?
- what alternatives can be considered?
- are there any clinical trials that I should consider?

11.3 SOURCES OF FURTHER INFORMATION FOR PATIENTS AND CARERS

Barrett's Oesophagus Foundation

University Department of Surgery, Royal Free and University College Medical School,
Rowland Hill Street, London NW3 2PF
Tel: 020 7472 6223 • Fax: 020 7472 6224
Email: enquiries@barrettsfoundation.org.uk

CancerBACUP Scotland

Suite 2, 3rd Floor, Cranston House, 104-114 Argyle Street, Glasgow, G2 8BH
Tel: 0141 223 7676 • Fax: 0141 248 8422 • FREEPHONE: 0808 800 1234
Email: info@cancerbacup.org • www.cancerbacup.org.uk

Cancer Research UK

PO Box 123, Lincoln's Inn Fields, London, WC2A 3PX
Tel: 020 7242 0200 • 020 7121 6699 (supporter services) • Fax: 0207 269 3100
www.cancerresearchuk.org

CORE

3 St Andrew's Place, London, NW1 4LB
Tel: 020 7486 0341 • Fax: 020 7224 2012
Email: info@corecharity.org.uk • www.corecharity.org.uk

Macmillan Cancer Relief Scotland

Osborne House, 1-5 Osborne Terrace, Edinburgh, EH1 2DP
Tel: 0131 346 5346 • Fax: 0131 346 5347 • Helpline: 0808 808 2020
Email: osni@macmillan.org.uk • www.macmillan.org.uk

Maggie's Dundee

Ninewells Hospital, Tom MacDonald Avenue, Dundee DD2 1ZV
Tel: 01382 496384
Email: valerie@maggiescentres.org • www.maggiescentres.org

Maggie's Edinburgh

The Stables, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU
Tel: 0131 537 3131 • Fax: 0131 537 3130
Email: fionam@maggiescentres.org • www.maggiescentres.org

Maggie's Glasgow

The Gatehouse, Dumbarton Road, Glasgow, G11 6PA
Tel: 0141 330 3311 • Fax: 0141 330 3363
Email: jillian@maggiescentres.org • www.maggiescentres.org

Maggie's Highlands

Raigmore Hospital, Inverness IV2 3UJ
Tel: 01463 706 306
Email: highlands@maggiescentres.org • www.maggiescentres.org

Marie Curie Cancer Care Scotland

29 Albany Street, Edinburgh, EH1 3QN
Tel: 0131 456 3700
www.mariecurie.org.uk

National Cancer Research Network

NCRN Co-ordinating Centre, Arthington House,
Cookridge Hospital, Hospital Lane, Leeds, LS16 6QB
Email: enquiries@ncrn.org.uk • www.ncrn.org.uk

Ochre (Oesophageal Cancer Has Reached Everywhere)

Eaton Place, Glasgow, G61 2RP
Tel: 0141 942 5855
Email: mailbox@ochre-charity.co.uk • www.ochrecharity.co.uk/

Oesophageal Patients Association

22 Vulcan House, Vulcan Road, Solihull, B912JY
Tel: 0121 704 9860
Email: opa@ukgateway.net • www.opa.org.uk

Tak Tent Cancer Support

Flat 5, 30 Shelley Court, Gartnavel Complex, Glasgow, G12 0YN
Tel: 0141 211 0122, Fax • 0141 211 3988
Email: tak.tent@care4free.net • www.taktent.org.uk

12 Implementation, audit and resource implications

12.1 LOCAL IMPLEMENTATION AND MANAGED CLINICAL NETWORKS

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

Three regional managed clinical networks (MCNs) for upper GI cancer are in place to ensure equitable provision of high quality clinically effective services throughout Scotland.³⁹³ These MCNs also cover hepatic, pancreatic and biliary cancers. The implementation of this guideline by the regional MCNs will facilitate their role in bringing about demonstrable improvement in patient outcomes. The MCNs' role in promoting equitable access to specialist services for patients with potentially curable disease and improved selection for and local delivery of palliative therapies is central to this process.

12.2 KEY POINTS FOR AUDIT

Audit of the patient journey and clinical outcomes is integral to improving care for patients with oesophageal and gastric cancer.

- Implementation of a nationally acceptable minimum dataset should be supported and resourced on a Scotland wide basis
- All patients diagnosed with oesophageal or gastric cancer should be entered into clinical audit
- Clinicians and multidisciplinary teams should be aware of their individual outcomes with oesophageal or gastric cancer patients
- The three upper GI cancer clinical networks in Scotland should review and quality assure audit data nationally with a view to setting standards and ultimately removing regional differences in care
- Clinical audit of patients with potentially curable disease should emphasise medium and long term outcomes
- For patients with incurable disease at time of diagnosis the audit process should emphasise quality of life and symptom palliation.

12.3 RECOMMENDATIONS FOR RESEARCH

12.3.1 DIAGNOSIS AND REFERRAL

- Investigation of potential screening strategies for at-risk patients
- Large prospective randomised controlled trials involving potentially high risk groups of gastro-oesophageal reflux patients to evaluate whether factors such as age, duration and severity of symptoms, smoking and BMI can be used to identify patients as being at high risk of oesophageal or gastric cancer
- Evaluation of emerging endoscopic imaging technologies aimed at earlier diagnosis
- Assessment of the benefit/risk balance in use of aspirin or NSAIDs for prevention of oesophageal and gastric cancer.

12.3.2 ASSESSMENT AND STAGING

- Assessment of comorbidity in newly diagnosed oesophageal and gastric cancer patients and its influence on treatment decisions
- Preoperative risk scoring for mortality/morbidity
- Role of peritoneal cytology in laparoscopically 'clean' patients
- Assessment of the role of PET scanning in patients otherwise staged with potentially curable disease
- Preoperative risk stratification of stage III disease with respect to survival
- The role of the clinical nurse specialist in the delivery of patients needs' during the assessment and staging phase of management
- Prediction of tumour response to neoadjuvant therapy
- Appropriate staging algorithms for patients with oesophagogastric junctional tumours.

12.3.3 TREATMENT WITH CURATIVE INTENT

- A randomised trial of radical chemoradiotherapy versus surgery for patients with squamous cancer of the middle third of the oesophagus
- Investigation of minimally invasive laparoscopic/thoroscopic techniques for gastric and oesophageal surgery
- Trials aimed at optimising preoperative treatment of oesophageal cancer and perioperative treatment of gastric cancer; including the investigation of conventional chemotherapy drugs, novel anticancer agents, immunotherapy and the use of intraperitoneal chemotherapy
- The role of non-surgical curative treatments for superficial oesophageal cancer and early gastric cancer
- Investigation into the optimum perioperative management including fluid therapy in the immediate postoperative period
- Quality of life in survivors after surgical resection and the impact of survival duration on return to normal quality of life.

12.3.4 TREATMENT WITH PALLIATIVE INTENT

- Quality of life and the impact of degree of dysphagia and relief of dysphagia – a comparison of the different available treatment options
- Investigation of delays in obtaining access to palliation of dysphagia after the initial diagnostic stage
- Investigation of regional variation in the use of invasive therapies
- Definition of the role of new agents, including molecular targeted therapies, in combination with existing chemotherapy regimens as first line palliative chemotherapy treatments
- Investigation of the role of the cancer nurse specialist in facilitating patient access to palliative services
- Patient outcomes as a consequence of access to a clinical nurse specialist
- Investigation of the most appropriate hospital setting for access to therapeutic endoscopy in the palliation of symptoms, local hospital versus specialist centre
- Comparison of laparoscopic with the open surgical approach to bypass and to compare laparoscopic with ablative and intubative techniques. Validated QoL measures should be used as primary end points
- Interventional techniques should be compared with non-interventional medical therapy advised by a palliative care team
- Definition of role of second line palliative chemotherapy
- Treatment approaches combining multiple modalities require further study
- In view of the cost implications of the widespread use of erythropoietin, further studies are encouraged to determine the clinical and economic benefits of this agent compared with traditional methods of care
- RCTs on the use of argon beam coagulation in control of obstructive symptoms.

12.3.5 SUPPORTIVE CARE

- Demonstration of the effect of nutritional assessment and intervention in the oesophageal and gastric cancer populations
- Identify causes of cancer cachexia and effective treatment strategies for oesophageal and gastric cancer patients including further evaluation of the role of thalidomide
- Investigation of the different models of specialist palliative care
- What are the supportive care needs of patients with oesophageal cancer and their carers?
- The role and impact of the clinical nurse specialist on patient quality of life
- What are the key factors which affect the quality of life of patients with oesophageal and gastric cancer and their carers and how can they be influenced

12.4 RESOURCE IMPLICATIONS OF RECOMMENDATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementing the recommendations made in the guideline. Where current practice will not change as a result of the recommendations it is unlikely there will be resource implications.

The following table shows those recommendations most likely to have significant resource implications across Scotland.

The resource implications associated with good practice points have not been considered. Resource implications of many of the recommendations are linked through the issue of potential centralisation of specialist services and are difficult to predict. These are highlighted (♦).

4.2	C	Flexible upper GI endoscopy is recommended as the diagnostic procedure of choice in patients with suspected oesophageal or gastric cancer.	Diagnostic endoscopy services will require expansion to replace existing barium service. Expansion must be sufficient to minimise delay in diagnosis.
4.3.2♦	C	Where radical intervention is contemplated on the basis of high grade dysplasia or early adenocarcinoma the diagnosis should be validated by a second pathologist experienced in this area and further biopsies should be taken if there is uncertainty.	Input from at least two specialist GI pathologists will be required in each major centre.
5.1.1	B	In patients with oesophageal or gastric cancer CT scan of the chest and abdomen with intravenous contrast and gastric distension with oral contrast or water should be performed routinely. The liver should be imaged in the portal venous phase.	Many patients do currently undergo CT. Need for increased capacity and improved quality with up-to-date equipment and sufficient service to avoid delays.
5.1.2♦	B	Patients with oesophageal or oesophagogastric junction cancers who are candidates for any curative therapy should have their tumours staged with endoscopic ultrasound +/- fine needle aspiration.	Increased availability of EUS equipment and trained staff to provide EUS for all patients considered for curative treatment.
5.4.1	B	Resection specimens of oesophageal and gastric cancer resections should be reported according to, or supplemented by, the Royal College of Pathologists' minimum data sets.	Need for increased pathology resource.
6.3	D	Follow up of patients with oesophageal or gastric cancer should monitor symptoms, signs and nutritional status.	Need for increased clinical nurse specialist and dietetic support.
7.2.3♦	B	Oesophageal and gastric cancer resectional surgery should be carried out in high volume specialist surgical units by frequent operators.	Reallocation of staff to larger hospitals. Improved provision of ITU service in designated centres. Need for reallocation of pathology resource. Possibly fewer resections.
7.7	B	Patients undergoing surgery for oesophageal or gastric cancer who are identified as being at high nutritional risk should be considered for preoperative nutritional support.	Need for increased specialist dietetic support.
	B	All patients undergoing surgery for oesophageal or gastric cancer should be considered for early postoperative nutritional support preferably by the enteral route.	
7.8.1♦	C	The assessment and management of patients with high grade dysplasia should be centralised to units with the appropriate endoscopic facilities and expertise.	Need for reallocation of pathology resource.
8.1.1	B	Patients with operable oesophageal cancer, who are treated surgically, should be considered for two cycles of preoperative chemotherapy with cisplatin and 5-fluorouracil or offered entry into a clinical trial.	Need for improved access to preoperative treatment with timing of surgery to avoid delays. Staffing resource issue.
9.1	C	Chemoradiotherapy should be considered in patients with oesophageal cancer who have locally advanced disease, those unfit for surgery or those who decline surgery.	More patients will require chemoradiotherapy services. Increased resource required for chemotherapy nursing and radiographers.
10.5	B	Laser or photodynamic therapy should be used for initial control of obstructive symptoms caused by exophytic tumours in the oesophagus including tumours near the upper oesophageal sphincter.	Centres providing palliative services for these cancers should have access to a range of laser / ablative therapies with availability of brachytherapy where required. Resource implications will depend on current local service provision.
10.5	D	Laser or photodynamic therapy should be considered for control of tumour overgrowth in stented patients	
10.9.4	D	Endoluminal brachytherapy is an option for patients with dysphagia from oesophageal cancer.	

13 Development of the guideline

13.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practicing clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

13.2 THE GUIDELINE DEVELOPMENT GROUP

Mr Robert C Stuart (Chair)	<i>Senior Lecturer in Surgery, Glasgow Royal Infirmary</i>
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Ms Joanna Welsh	<i>Information Officer, SIGN</i>
Mr Barry W A Williamson	<i>Consultant in General Surgery, Royal Alexandra Hospital, Paisley</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

13.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using a search strategy devised by a SIGN Information Officer. Databases searched include Medline, Embase, Cinahl, PsychINFO, and the Cochrane Library. For most searches, the year range covered was 1994-2004. Internet searches were carried out on various websites including the New Zealand Guidelines Programme, NELH Guidelines Finder, and the US National Guidelines Clearinghouse. The Medline version of the main search strategies can be found on the SIGN website, in the section covering supplementary guideline material. The main searches were supplemented by material identified by individual members of the development group.

13.4 CONSULTATION AND PEER REVIEW

13.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held in February 2005 and was attended by 181 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

13.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Douglas Adamson	<i>Consultant Clinical Oncologist, Ninewells Hospital, Dundee</i>
Professor Derek Alderson	<i>Professor of Gastrointestinal Surgery, Bristol Royal Infirmary</i>
Mr William Allum	<i>Consultant Surgeon, Royal Marsden Hospital, London</i>
Dr Alan G Begg	<i>General Practitioner, Townhead Practice, Montrose</i>
Professor Frank A Carey	<i>Clinical Leader in Pathology, Ninewells Hospital, Dundee</i>
Professor David Cunningham	<i>Specialist in Gastrointestinal Cancer and Lymphoma, Royal Marsden Hospital, Surrey</i>
Professor Jeff Evans	<i>Senior Lecturer and Honorary Consultant in Medical Oncology, Beatson Laboratories, Glasgow</i>
Dr Grant Fullarton	<i>Consultant Surgeon, Gartnavel General Hospital, Glasgow</i>

Dr Dermot Gorman	<i>Consultant in Public Health, Lothian NHS Board, Edinburgh</i>
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Dr David Johnston	<i>Consultant Gastroenterologist, Ninewells Hospital, Dundee</i>
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Dr Gordon M Pringle	<i>General Practitioner, Ardach Health Centre, Buckie</i>
Dr Sheila Rankin	<i>Consultant Radiologist, Guy's Hospital, London</i>
Dr John Reid	<i>Divisional Medical Director, Forth Valley Acute Operating Division Headquarters, Falkirk</i>
Professor Alastair M Thompson	<i>Professor of Surgical Oncology, Ninewells Hospital, Dundee</i>
Dr Shaun Walsh	<i>Consultant Pathologist, Ninewells Hospital, Dundee</i>
Dr Ian Zealley	<i>Consultant Radiologist, Ninewells Hospital, Dundee</i>

13.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows.

Dr David Alexander	<i>Scottish General Practice Committee</i>
Dr James Beattie	<i>Royal College of General Practitioners</i>
Mr Andrew de Beaux	<i>Royal College of Surgeons, Edinburgh</i>
Dr Graham Howard	<i>Royal College of Radiologists, Faculty of Oncology</i>
Dr John Kinsella	<i>Royal College of Anaesthetists</i>
Professor Gordon Lowe	<i>Chair of SIGN; Co-Editor</i>
Dr Safia Qureshi	<i>SIGN Programme Director; Co-Editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>
Ms Susan Watt	<i>Royal College of Nursing</i>

13.5 ACKNOWLEDGEMENTS

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of this guideline.

Dr Alistair Lee	<i>Consultant Anaesthetist, Royal Infirmary of Edinburgh</i>
Ms Ailsa Stein	<i>Information Officer, SIGN</i>
Ms Diane Stockton	<i>Statistician, ISD, Edinburgh</i>

Abbreviations

5-FU	Fluorouracil
APC	Argon plasma coagulation
ARDS	Adult respiratory distress syndrome
ASA	American Society of Anesthesiologists
BMI	Body mass index
BUS	Bronchoscopic ultrasound
CI	Confidence interval
CNS	Clinical nurse specialist
CPB	Coeliac axis plexus block
CT	Computerised tomography
ECF	Epirubicin, cisplatin, fluorouracil
EMR	Endoscopic mucosal resection
EN	Enteral nutrition
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Eicosapentanoic acid
EPO	Erythropoietin
EUS	Endoscopic ultrasound
FACT	Functional assessment of cancer therapy
FAM	5-FU, adriamycin, mitomycin-C
FAMTX	5-fluorouracil, doxorubicin and methotrexate
FEV1	Forced expiratory volume in the first one second
FNA	Fine needle aspiration
FVC	Forced vital capacity
GI	Gastrointestinal
GP	General Practitioner
Gy	Gray
HGD	High grade dysplasia
MAGIC	MRC Adjuvant Gastric Infusional Chemotherapy trial
MCF	Mitomycin C, cisplatin, fluorouracil
MCN	Managed clinical network
MDM	Multidisciplinary meeting
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
Nd-YAG	Neodymium-yttrium aluminium garnet
NEF	Nasoenteric feeding
NHSQIS	National Health Service Quality Improvement Scotland
NSAIDs	Non-steroidal anti-inflammatory drugs

NNT	Number needed to treat
OR	Odds ratio
PDT	Photodynamic therapy
PEG	Percutaneous endoscopic gastroscopy
PET	Positron emission tomography
PN	Parenteral nutrition
POSSUM	Physiological and operative severity score for the enumeration of mortality and morbidity
QoL	Quality of life
RCP	Royal College of Pathologists
RCT	Randomised controlled trial
RIG	Radiological inserted gastrostomy
SAGOC	Scottish audit of gastric and oesophageal cancer
SEMS	Self expanding metal stents
SEPS	Self expanding plastic stents
SIGN	Scottish Intercollegiate Guidelines Network
TNM	Tumour, nodes, metastases
TPN	Total parenteral nutrition
UICC	International Union Against Cancer
UGIE	Upper gastrointestinal endoscopy
US	Ultrasound
USA	United States of America
WHO	World Health Organisation

Annex 1

Vienna classification of gastrointestinal epithelial neoplasia

- Category 1 Negative for neoplasia/dysplasia
- Category 2 Indefinite for neoplasia/dysplasia
- Category 3 Non-invasive low grade neoplasia
(low grade adenoma/dysplasia)
- Category 4 Non-invasive high grade neoplasia
 - 4.1 High grade adenoma/dysplasia
 - 4.2 Non-invasive carcinoma (carcinoma in situ)*
 - 4.3 Suspicion of invasive carcinoma
- Category 5 Invasive neoplasia
 - 5.1 Intramucosal carcinoma
 - 5.2 Submucosal carcinoma or beyond

*Non-invasive indicates absence of evident invasion.

Annex 2

TNM classification of malignant tumours 6th edition¹¹²

TNM Clinical Classification Oesophagus

Primary Tumour (T)

- TX Primary tumour cannot be assessed
 T0 No evidence of primary tumour
 Tis Carcinoma in situ
 T1 Tumour invades lamina propria or submucosa
 T2 Tumour invades muscularis propria
 T3 Tumour invades adventitia
 T4 Tumour invades adjacent structures

Lymph node (N)

- NX Regional lymph nodes cannot be assessed
 N0 No regional lymph node metastasis
 N1 Regional lymph node metastasis

Distant metastasis (M)

- MX Presence of distant metastasis cannot be assessed
 M0 No distant metastasis
 M1 Distant metastasis

For tumours of lower thoracic oesophagus

M1a Metastasis in coeliac lymph nodes

M1b Other distant metastasis

For tumours of the upper thoracic oesophagus

M1a Metastasis in cervical lymph nodes

M1b Other distant metastasis

For tumours of mid-thoracic oesophagus

M1a Not applicable

M1b Non-regional lymph node or other distant metastasis

In cases where there has been preoperative multimodality therapy this should be indicated in the pathological staging and may be noted by the 'y' prefix.

Oesophageal Cancer Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2, T3	N0	M0
Stage IIB	T1,T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

TNM Clinical Classification Stomach**Primary Tumour (T)**

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: Intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria or subserosa
T2a	Tumour invades muscularis propria
T2b	Tumour invades subserosa
T3	Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumour invades adjacent structures

Lymph node (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

In cases where there has been preoperative multimodality therapy this should be indicated in the pathological staging and may be noted by the 'y' prefix.

Gastric Cancer Stage Groupings			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2a/b	N0	M0
Stage II	T1	N2	M0
	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

Annex 3

National minimum dataset oesophageal carcinoma histopathology report

Surname Forenames Date of birth Sex
 Hospital Hospital No NHS No
 Date of receipt Date of reporting Report No
 Pathologist Surgeon

Gross description

Maximum length of specimen: mm pinned not pinned
 Length of oesophagus: mm Length of stomach (maximum): mm
 Width of tumour: mm Length of tumour: mm
 Tumour edge to nearest distal margin: mm
 Tumour edge to nearest proximal margin: mm
 Macroscopic type of tumour polypoid other

Histology

Type of tumour:

squamous
 adenocarcinoma
 other (specify)
 differentiation by predominant area:
 well moderately poorly differentiated

Depth of invasion:

Tis high grade dysplasia
 T1 invasion of lamina propria / submucosa
 T2 invasion of muscularis propria
 T3 invasion beyond muscularis propria
 T4 invasion of adjacent structures

serosal involvement: yes no

Proximal margin:

normal Barrett's dysplasia carcinoma
 (M1a if upper thoracic carcinoma, otherwise M1b)

Circumferential margin:

involvement (>1mm): yes no
 (if no - distance of carcinoma to nearest
 circumferential margin mm)

Distal margin features

normal dysplasia carcinoma

Other features

vascular invasion yes no
 Barret's metaplasia yes no
 adjacent to tumour

Lymph Nodes

number examined Number positive
 (N0 if no nodes positive, otherwise N1)

Distant metastases:

coeliac axis node positive: yes no
 (M1a if lower thoracic carcinoma, otherwise M1b)
 cervical node positive: yes no
 other distant metastasis (M1b) yes no

Comments

Pathological staging

complete resection at all margins yes no pT pN pM

Signature Date
 SNOMED Codes T M

Source: www.rcpath.org/index.asp?PageID=254

Annex 4

National minimum dataset gastric cancer histopathology report

Surname Forenames Date of birth Sex
 Hospital Hospital No NHS No
 Date of request Date of reporting Report No
 Pathologist Surgeon

Gross description

Type of specimen: Gastrectomy Total Subtotal Partial
 Oesophago-gastrectomy
 Spleen included Pancreas included
 Length of specimen – lesser curve.....mm Length of specimen – greater curve.....mm
 Length of duodenum.....mm Length of oesophagus.....mm
 Site of tumour: Pylorus Antrum Body O-G junction
 Lesser curve Greater curve Anterior wall Posterior wall
 Macroscopic type: Ulcer like Diffusely infiltrating Fungating Polypoid
 Size of tumour: Length.....mm Width.....mm Thickness.....mm
 Distance of tumour edge to: Distal margin.....mm Proximal margin.....mm

Histology

Adenocarcinoma: Yes No Other (specify)
 Differentiation: Poor Other
 Character of the invasive margin: Expansive Infiltrative

Local Invasion into:

Lamina propria (Intra-mucosal) (T1) Submucosa (T1)
 Muscularis propria (T2) Subserosa (T2)
 Tumour penetrates peritoneum without invasion of adjacent structures (T3)
 Tumour invades adjacent structures (T4) → structure invaded.....

Lymph Node Spread: Regional

Lymph Node Spread: Distant

Total number of regional lymph nodes examined..... Nodes submitted separately from:
 Number of lymph nodes involved..... Number submitted.....Number involved.....[M1]
 (0 involved = N0; 1-6 involved = N1; 7-15 involved = N2; >15 involved = N3)

Other Sites:

Histologically confirmed liver metastasis: Yes No Peritoneal deposits Yes No
 Margins: Tumour involvement of: Proximal donut Yes No Distal donut Yes No
 Proximal margin Main specimen Yes No Frozen section Yes No
 Distal margin Main specimen Yes No Frozen section Yes No

Other Pathology

Chronic gastritis: Yes No Atrophy Yes No
 Intestinal metaplasia: Yes No *H.pylori* Yes No
 Other lesions: Yes No Lesion present.....
 Synchronous carcinoma Yes No If yes, please fill out a second form

Comments

Pathological Staging

Complete resection at all margins? Yes No pTNM: pT pN pM

Signature:Date: SNOMED codes:

Source: www.rcpath.org/index.asp?PageID=254

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PRESENTATION AND REFERRAL

B	A test and treat policy for <i>Helicobacter pylori</i> should be employed in the initial management of patients with uncomplicated dyspepsia.
C	Irrespective of age, patients should be reviewed after <i>Helicobacter pylori</i> eradication treatment. For those with recurrent or persistent symptoms the need for further assessment, including endoscopy, should be considered.
C	In patients with gastro-oesophageal reflux symptoms, endoscopy with the intention of identifying cancer is not indicated unless an alarm symptom is also present.
<p>▶ Alarm symptoms</p>	
B	Patients presenting with any of the following alarm symptoms should be referred for early endoscopy: <ul style="list-style-type: none"> ▪ dysphagia ▪ recurrent vomiting ▪ anorexia ▪ weight loss ▪ gastrointestinal blood loss.

DIAGNOSIS

C	Flexible upper GI endoscopy is recommended as the diagnostic procedure of choice in patients with suspected oesophageal or gastric cancer.
D	Routine use of chromoendoscopy during upper GI endoscopy is not recommended, but may be of value in selected patients at high risk of oesophageal or gastric malignancy.
C	A minimum of eight biopsies should be taken to achieve a diagnosis of oesophageal malignancy.

STAGING MODALITIES

B	In patients with oesophageal or gastric cancer CT scan of the chest and abdomen with intravenous contrast and gastric distension with oral contrast or water should be performed routinely. The liver should be imaged in the portal venous phase.
B	Patients with oesophageal or oesophagogastric junction cancers who are candidates for any curative therapy should have their tumours staged with endoscopic ultrasound +/- fine needle aspiration.

STAGING MODALITIES (Contd.)

C	Laparoscopy should be considered in patients with oesophageal tumours with a gastric component, and in patients with gastric tumours being considered for surgery where full thickness gastric wall involvement is suspected.
C	MRI should be reserved for those patients who cannot undergo CT, or used for additional investigation following CT/EUS.
D	Bronchoscopy +/- BUS +/- biopsy should be undertaken in patients with clinical or imaging features suspicious of tracheobronchial invasion.
D	Thoracoscopy may be considered for patients where a tissue diagnosis of suspicious nodes (not possible by either EUS or CT guided techniques) is required to determine optimum management.
C	PET is not routinely indicated in the staging of oesophageal and gastric cancers.
D	Neck imaging either by US or CT is recommended as part of the staging of oesophageal cancer.

SIGNIFICANCE OF TUMOUR STAGE

<p>▶ Treatment and survival</p>	
B	Patients with gastric or oesophageal cancer should undergo careful preoperative staging to enable targeting of potentially curative treatment to those likely to benefit.
B	Patients with gastric or oesophageal cancer who have distant metastases or patients with oesophageal cancer who have metastatic lymph nodes in three compartments (<i>neck, mediastinum and abdomen</i>) on preoperative staging are not candidates for curative treatment.

C	When M1a nodal involvement in oesophageal cancer, or extensive lymphadenopathy in any cancer, is identified on preoperative staging, the anticipated poor prognosis should be carefully considered when discussing treatment options.
<p>▶ Surgery and quality of life</p>	
☑	Where there is clear evidence of incurable disease following staging, attempts at resection should be avoided.

D	The possibility of reduction in quality of life after surgery should be considered when discussing treatment options, particularly when preoperative staging suggests that surgery would be unlikely to be curative.
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SURGERY

B	All patients being considered for surgery should undergo careful assessment of fitness with emphasis on performance status and respiratory function.
B	Surgery for oesophageal or gastric cancer should be aimed at achieving an R0 resection (<i>proximal, distal and circumferential margin clearance</i>).
B	Oesophageal and gastric cancer resectional surgery should be carried out in high volume specialist surgical units by frequent operators.
<p>FOLLOW UP</p>	
D	Follow up of patients with oesophageal or gastric cancer should monitor symptoms, signs and nutritional status.
<p>PALLIATIVE CARE</p>	
C	Patients with oesophageal or gastric cancer should have access to a specialist palliative care team.

Invasive palliative treatments

☑	Selection of patients for invasive palliative interventions should be carried out by a multidisciplinary team. There should be integration of the acute multidisciplinary team and the palliative care team to ensure appropriate continuous palliative care.
B	Laser or photodynamic therapy should be used for initial control of obstructive symptoms caused by exophytic tumours in the oesophagus including tumours near the upper oesophageal sphincter.
D	Laser or photodynamic therapy should be considered for control of tumour overgrowth in stented patients.
B	Partially covered self expanding metal stents are the intubation of choice for patients with obstructive oesophageal symptoms.
C	Partially covered self expanding metal stents should be used to control obstructive oesophageal symptoms either following or instead of laser therapy, depending on the availability of local expertise.
D	The use of oesophageal dilatation alone should be avoided.