Guidelines for the management of oesophageal and gastric cancer

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INTRODUCTION

Over the past decade the Improving Outcomes Guidance (IOG) document has led to service re-configuration in the NHS and there are now 41 specialist centres providing oesophageal and gastric cancer care in England and Wales. The National Oesophago-Gastric Cancer Audit, which was supported by the British Society of Gastroenterology, the Association of Upper Gastrointestinal Surgeons (AUGIS) and the Royal College of Surgeons of England Clinical Effectiveness Unit, and sponsored by the Department of Health, has been completed and has established benchmarks for the service as well as identifying areas for future improvements.[1–3] The past decade has also seen changes in the epidemiology of oesophageal and gastric cancer. The incidence of lower third and oesophago-gastric junctional adenocarcinomas has increased further, and these tumours form the most common oesophago-gastric tumour, probably reflecting the effect of chronic gastro-oesophageal reflux disease (GORD) and the epidemic of obesity. The increase in the elderly population with significant co-morbidities is presenting significant clinical management challenges. Advances in understanding of the natural history of the disease have increased interest in primary and secondary prevention strategies. Technology has improved the options for diagnostic and therapeutic endoscopy and staging with cross-sectional imaging. Results from medical and clinical oncology trials have established new standards of practice for both curative and palliative interventions. The quality of patient experience has become a significant component of patient care, and the role of the specialist nurse is fully intergrated. These many changes in practice and patient management are now routinely controlled by established multidisciplinary teams (MDTs) which are based in all hospitals managing these patients.

STRUCTURE OF THE GUIDELINES

The original guidelines described the management of oesophageal and gastric cancer within existing practice. This paper updates the guidance to include new evidence and to embed it within the framework of the current UK National Health Service (NHS) Cancer Plan.[4] The revised guidelines are informed by reviews of the literature and collation of evidence by expert contributors.[5] The key recommendations are listed. The sections of the guidelines are broadly the same layout as the earlier version, with some evidence provided in detail to describe areas of development and to support the changes to the recommendations. The editorial group (WHA, JMB, DC, JAJ, SMG and RW) have edited the individual sections, and the final draft was submitted to independent expert review and modified. The strength of the evidence was classified guided by standard guidelines.[6]

Categories of evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials (RCTs).
Ib: Evidence obtained from at least one randomised trial.
IIa: Evidence obtained from at least one well-designed controlled study without randomisation.
IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study.
III: Evidence obtained from well-designed descriptive studies such as comparative studies, correlative studies and case studies.
IV: Evidence obtained from expert committee reports, or opinions or clinical experiences of respected authorities.

Grading of recommendations

Recommendations are based on the level of evidence presented in support and are graded accordingly.
Grade A requires at least one RCT of good quality addressing the topic of recommendation.
Grade B requires the availability of clinical studies without randomisation on the topic of recommendation.
Grade C requires evidence from category IV in the absence of directly applicable clinical studies.

SUMMARY OF RECOMMENDATIONS

Prevention

- There is no established chemoprevention role for upper gastrointestinal (UGI) cancer, and trials are currently assessing this (grade C).
- The role of surveillance endoscopy for Barrett's oesophagus or endoscopy for symptoms remains unclear, and trials are currently assessing this (grade B).

Diagnosis

- All patients with recent-onset 'dyspepsia' over the age of 55 years and all patients with alarm symptoms (whatever their age) should be referred for rapid access endoscopy with biopsy (grade C).

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- A minimum of six biopsies should be taken to achieve a diagnosis of malignancy in areas of oesophageal or gastric mucosal abnormality (grade B).
- Endoscopic findings of benign stricturing or oesophagitis should be confirmed with biopsy (grade C).
- Gastric ulcers should be followed up by repeat gastroscopy and biopsy to assess healing and exclude malignancy (grade B).
- Patients diagnosed with high grade dysplasia should be referred to an UGI MDT for further investigation (grade B).
- High resolution endoscopy, chromoendoscopy, spectroscopy, narrow band imaging and autofluorescence imaging are under evaluation and their roles are not yet defined (grade C).

Staging

- Staging investigations for UGI cancer should be co-ordinated within an agreed pathway led by a UGI MDT (grade C).
- Initial staging should be performed with a CT including multiplanar reconstructions of the thorax, abdomen and pelvis to determine the presence of metastatic disease (grade B).
- Further staging with endoscopic ultrasound in oesophageal, oesophago-gastric junctional tumours and selected gastric cancers is recommended, but it is not helpful for the detailed staging of mucosal disease (grade B).
- For T1 oesophageal tumours or nodularity in high grade dysplasia, staging by endoscopic resection should be used to define depth of invasion (grade B).
- Positron emission tomography (PET)-CT scanning should be used in combination with endoscopic ultrasound (EUS) and CT for assessment of oesophageal and oesophago-gastric junctional cancer (grade B).
- Laparoscopy should be undertaken in all gastric cancers and in selected patients with lower oesophageal and oesophago-gastric junctional tumours (grade C).

Pathology

- Diagnosis of high grade dysplasia in the oesophagus and stomach should be made and confirmed by two histopathologists, one with a special interest in gastrointestinal disease (grade C).
- Reports on oesophageal and gastric resection specimens should concur with the Royal College of Pathologists (RCPath) (grade B).
- Oesophago-gastric junctional tumours should be classified as type I (distal oesophageal), type II (cardia) and type III (proximal stomach) (grade C).

Treatment: decision-making

- Treatment recommendations should be undertaken in the context of a UGI MDT taking into account patient co-morbidities, nutritional status, patient preferences and staging information. Recommendations made by the MDT should be discussed with patients within the context of a shared decision-making consultation (grade C).

Treatment: endoscopy

- Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can eradicate early gastro-oesophageal mucosal cancer. EMR should be considered in patients with oesophageal mucosal cancer and both EMR and ESD should be considered for gastric mucosal cancer (grade B).
- The role of EMR in patients with macroscopic abnormalities within Barrett's oesophagus and ablation of residual areas of dysplasia requires further research (grade C).

Treatment: surgery

- All patients should have antithrombotic (grade A, 1b) and antibiotic prophylaxis (grade C) instituted at an appropriate time in relation to surgery and postoperative recovery.
- Oesophageal and gastric cancer surgery should be performed by surgeons who work in a specialist MDT in a designated cancer centre with outcomes audited regularly (grade B).
- Surgeons should perform at least 20 oesophageal and gastric resections annually either individually or operating with another consultant both of whom are core members of the MDT. The individual surgeon and team outcomes should be audited against national benchmarked standards (grade B).

Treatment: oesophageal resection

- There is no evidence favouring one method of oesophageal resection over another (grade A), and evidence for minimal access techniques is limited (grade C).
- The operative strategy should ensure that adequate longitudinal and radial resection margins are achieved with lymphadenectomy appropriate to the histological tumour type and its location (grade B).

Treatment: gastric resection

- Distal (antral) tumours should be treated by subtotal gastrectomy and proximal tumours by total gastrectomy (grade B).
- Cardia, subcardia and type II oesophago-gastric junctional tumours should be treated by transhiatal extended total gastrectomy or oesophago-gastrectomy (grade B).
- Limited gastric resections should only be used for palliation or in the very elderly (grade B).
- The extent of lymphadenectomy should be tailored to the age and fitness of the patient together with the location and stage of the cancer (grade C).
- Patients with clinical stage II and III cancers of the stomach should undergo a D2 lymphadenectomy if fit enough (grade A; Ib).
- The distal pancreas and spleen should not be removed as part of a resection for a cancer in the distal two-thirds of the stomach (grade A; Ib).
- The distal pancreas should be removed only when there is direct invasion and still a chance of a curative procedure in patients with carcinoma of the proximal stomach (grade A; Ib).
- Resection of the spleen and splenic hilar nodes should only be considered in patients with tumours of the proximal stomach located on the greater curvature/posterior wall of the stomach close to the splenic hilum where the incidence of splenic hilar nodal involvement is likely to be high (grade C).

Treatment: chemotherapy and radiotherapy

Oesophageal squamous cell carcinoma

- There is no evidence to support the use of preoperative radiotherapy in oesophageal squamous cell carcinoma (grade A; Ia).
- Chemoradiation is the definitive treatment of choice for localised squamous cell carcinoma of the proximal oesophagus (grade A; Ia).
- Localised squamous cell carcinoma of the middle or lower third of the oesophagus may be treated with chemoradiotherapy alone or chemoradiotherapy plus surgery (grade A; Ib).
- There is no evidence to support routine use of adjuvant chemotherapy in oesophageal squamous cell carcinoma (grade A; Ia).

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Oesophageal adenocarcinoma (including type I, II and III oesophago-gastric junctional adenocarcinoma)

- Preoperative chemoradiation improves long-term survival over surgery alone (grade A; Ia).
- There is no evidence to support the use of preoperative radiotherapy in oesophageal adenocarcinoma (grade A; Ia).
- Preoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU) improves long-term survival over surgery alone (grade A; Ia).
- Perioperative chemotherapy (combined preoperative and postoperative) conveys a survival benefit and is the preferred option for type II and III oesophago-gastric junctional adenocarcinoma (grade A; Ib).

Gastric adenocarcinoma

- Perioperative combination chemotherapy conveys a significant survival benefit and is a standard of care (grade A; Ib).
- Adjuvant chemotherapy alone is currently not standard practice for resected adenocarcinoma but has survival benefits in non-Western populations and should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy (grade A; Ia).
- Adjuvant chemoradiotherapy improves survival and is a standard of care in the USA, and should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy (grade A; Ib).
- Intraperitoneal chemotherapy remains investigational (grade B).

Palliative treatment

- Palliative treatment should be planned by the MDT taking into account performance status and patient preference, with early direct involvement of the palliative care team and the clinical nurse specialist (CNS) (grade C).

Oesophageal cancer

- Palliative external beam radiotherapy can relieve dysphagia with few side effects, but the benefit is slow to achieve (grade B).
- Palliative brachytherapy improves symptom control and health-related quality of life (HRQL) where survival is expected to be longer than 3 months (grade A; Ib).
- Palliative chemotherapy provides symptom relief and improves HRQL in inoperable or metastatic oesophageal cancer (grade A; Ib).
- Palliative combination chemotherapy improves survival compared with best supportive care in oesophageal squamous cell carcinoma, adenocarcinoma and undifferentiated carcinoma (grade A; Ib).
- Trastuzumab in combination with cisplatin/fluoropyrimidine should be considered for patients with HER2-positive oesophago-gastric junctional adenocarcinoma as there is an improvement in disease-free survival (DFS) and overall survival (OS) (grade A; Ib).
- Oesophageal intubation with a self-expanding stent is the treatment of choice for firm stenosing tumours (capable of retaining an endoprosthesis), >2 cm from the cricopharyngeus, where rapid relief of dysphagia in a one-stage procedure is desirable, particularly for patients with a poor prognosis (grade B).
- Antireflux stents confer no added benefit above standard metal stents (grade A; Ib).
- Covered expandable metal stents are the treatment of choice for malignant tracheo-oesophageal fistulation or following oesophageal perforation sustained during dilatation of a malignant stricture (grade B).
- Laser treatment is effective for relief of dysphagia in exophytic tumours of the oesophagus and gastric cardia, and in treating tumour overgrowth following intubation (grade A; Ib).
- For patients whose dysphagia is palliated using laser therapy, the effect can be prolonged substantially by using adjunctive external beam radiotherapy or brachytherapy (grade A; Ib).
- Photodynamic therapy (PDT) is experimental and its use is not currently recommended (grade B).
- Argon plasma coagulation (APC) may be useful in treating overgrowth above and below stents and in reducing haemorrhage from inoperable tumours (grade C).
- There is no indication for local ethanol injection for symptom palliation (grade B).

Gastric adenocarcinoma

- Palliative combination chemotherapy for locally advanced and/or metastatic disease provides HRQL and survival benefit (grade A; Ia).
- Trastuzumab in combination with cisplatin/fluoropyrimidine should be considered for patients with HER2-positive gastric tumours as there is an improvement in DFS and OS (grade A; Ib).
- The use of other targeted agents should be confined to the context of clinical trials (grade B).
- Second-line irinotecan confers a small survival benefit over best supportive care (BSC), but is not currently approved by the National Institute for Health and Clinical Excellence (NICE) (grade A; Ib). Patients of good performance status should be considered for second-line chemotherapy in the context of clinical trials if available.

Follow-up

- There is a lack of UK-centred randomised evidence evaluating follow-up strategies (grade C).
- Audit should be structured with particular reference to outcome measures and should be regarded as a routine part of the work of the MDT (grade C).
- The development of a role for CNSs in follow-up should be actively pursued (grade C).

EPIDEMIOLOGY

Incidence

Over the past 20 years there has been an annual increase in incidence of adenocarcinoma of the oesophago-gastric junction in the UK. Demographically the peak age group affected is between 50 and 60 years of age, and the male to female ratio varies between 2:1 and 12:1. There have been parallel increases in adenocarcinoma of the gastric cardia, which now accounts for ~50% of all gastric cancers. The age group affected and the sex incidence are similar to those of adenocarcinoma of the lower oesophagus, suggesting a similar aetiology. Despite the rise in gastric cardia tumours, the incidence of gastric cancer is declining, with rates 11% lower in 2000 compared with 1990, because of a decreased incidence in distal gastric tumours.

Aetiology

The relationship between the development of oesophagogastric junctional cancer and chronic GORD is now well established. The risk associated with GORD is related to Barrett's metaplasia. There is also a three- to sixfold excess risk among overweight individuals.[7] Obesity predisposes to hiatus hernia and

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reflux, and hence contributes mechanically to increase risk. However, data from a number of studies demonstrate an effect independent of reflux. Lindblad and colleagues have reported a 67% increase in the risk of oesophageal adenocarcinoma in patients with a body mass index (BMI) >25, and this increases with increasing BMI. This effect was noted irrespective of the presence of reflux symptoms.[8] The increased risk was only found in obese women (BMI >30), whereas in men it was observed in both overweight (BMI 25–29.9) and obese (BMI >30) individuals. The Million Women study confirmed this effect, with 50% of cases of oesophageal adenocarcinoma in postmenopausal women being attributed to obesity.[9] Further evidence is accumulating to support different types of obesity, with the 'male pattern' of abdominal obesity (central and retroperitoneal) more likely to be associated with malignant transformation. This acts as a potent source of growth factors, hormones and regulators of the cell cycle, resulting in a predisposition to developing the metabolic syndrome. In the general population the metabolic syndrome occurs in 10–20%, and recent evidence demonstrated that 46% of those with Barrett's oesophagus and 36% of those with GORD have features of the metabolic syndrome. The factors released by centrally deposited fat may have an effect on the process of metaplasia transforming to dysplasia.[10]

The role of *Helicobacter pylori* infection in the aetiology of oesophago-gastric junctional cancer is evolving. The hypochlorhydria associated with *H pylori* in association with ammonia production from urea by the bacteria may protect the lower oesophagus by changing the content of the refluxing gastric juice. In countries with an increase in oesophago-gastric junctional cancer, there has been a corresponding decrease in incidence of *H pylori* infection. Furthermore, community-based approaches to eradicate *H pylori* infection in the treatment of ulcer and non-ulcer dyspepsia may be inadvertently contributing to the increase in these cancers.

Increases in incidence in true cardia (type II) and type III junctional cancers have parallelled the increase in type I cancers, and the natural history appears to be similar. Some consider the inflammation and metaplasia associated with cardia cancer to be caused by *H pylori* infection despite many cases presenting with reflux. Recently Hansen and colleagues have proposed that cardia cancer has two distinct aetiologies.[11] In a nested case–control study, serum from a defined population cohort followed for the development of gastric cancer was tested for *H pylori* antibodies and for evidence of atrophic gastritis using as surrogate markers gastrin levels and the pepsinogen I to pepsinogen II ratio. *H pylori* seropositivity and gastric atrophy were associated with the risk of non-cardia gastric cancer. In cardia cancer there were two distinct groups. In one, serology for *H pylori* was negative and there was no evidence of gastric atrophy, and in the other *H pylori* was positive and there was evidence of atrophy. The authors concluded that the former group behaved like non-cardia cancer and were more likely to be diffuse type, and the latter like oesophageal adenocarcinoma and likely to be intestinal type. Such different characteristics would imply a different carcinogenic process at the two sites.

Preventive strategies

Primary prevention is largely dependent on population education to alter social habits. A reduction in tobacco and alcohol consumption and an increase in a diet of fresh fruit and vegetables may reduce cancer incidence. Intervention trials to prove efficacy of these dietary strategies are lacking. In addition there is an enormous public health need to prevent obesity, which may lead to a reduction in incidence of UGI cancers. The role of *H pylori* eradication is important, although the potential paradoxical effect on oesophageal junctional adenocarcinoma needs further evaluation.

Secondary prevention strategies exploit the natural history and detection of premalignant conditions. Identification of p53 expression and aneuploidy in biopsies of Barrett's oesophagus has been shown to predict the risk of progression.[12] These biomarkers, however, are not validated for routine clinical use. Increasing levels of cyclo-oxygenase-2 (COX-2) in the mucosa are present in the progression of atrophic gastritis to intestinal metaplasia and gastric cancer. However, smoking, acid and *H pylori* are all associated with COX-2 expression. Recently it has been shown in colorectal cancer, with a similar trend in oesophageal adenocarcinoma, that the level of cytoplasmic β-catenin is directly proportional to survival (ie, low levels with poor survival and high levels with good survival).[13]

Aspirin and other non-steroidal agents inhibit COX-2 and could be chemopreventative for gastric cancer. Aspirin may have an effect in Barrett's metaplasia and, in combination with acid suppression, may minimise progression to dysplasia. The Aspirin Esomeprazole Chemoprevention Trial (AspECT trial) has successfully completed recruitment of 2513 patients into four arms (20 mg of esomeprazole alone, 80 mg of esomeprazole alone, 20 mg of esomeprazole with low dose aspirin and 80 mg of esomeprazole with low dose aspirin) and may demonstrate whether such a strategy can have a secondary cardiac and cancer preventive effect.[14] Currently advice about chemoprevention using aspirin cannot be given until this trial is complete in 2019. The role of surveillance is yet to be proven, and in this regard the Barrett's Oesophagus Surveillance Study is recruiting another 2500 patients to examine the role of 2-yearly endoscopy versus symptomatic need for endoscopy to reduce oesophageal adenocarcinoma. The role of host genetic susceptibility is shortly to be reported in a genome-wide assessment study called Inherited Predisposition to Oesophageal Diseases which is part of the UK-wide ChOPIN/EAGLE translational science infrastructure.[15]

DIAGNOSIS

Symptomatic presentation

The UK Department of Health has specified the 'at risk' symptoms for oesophago-gastric cancer which guide referral of patients for investigation and recommends urgent investigation to be performed within 2 weeks of referral.[16] In the Department of Health guide patients with new-onset dyspepsia are recommended urgent referral for gastroscopy only if they are over 55 years. However, early referral for more patients even with minimal symptoms should be considered because clinical diagnosis is often inaccurate and early tumours will not be associated with typical symptoms. Approximately 70% of patients with early gastric cancer (EGC) have symptoms of uncomplicated dyspepsia with no associated anaemia, dysphagia or weight loss.[17] It has recently been demonstrated that use of alarm symptoms to select patients for endoscopy causes patients with localised disease to be overlooked.[18] Clinical diagnosis is very inaccurate in distinguishing between organic and non-organic disease and therefore all patients deemed to be 'at risk' patients with dyspepsia should be considered for endoscopy even though the overall detection rate is only 1–3%.[19]

In summary, patients with dyspepsia who are older than 55 years of age with persistent new-onset symptoms or those with alarm features at any age should undergo an endoscopy. An endoscopy with biopsies should be considered for patients in whom there is a clinical suspicion of malignancy even in the absence of alarm features.

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Endoscopy

Video endoscopy and endoscopic biopsy remain the investigations of choice for diagnosis of oesophageal and gastric cancer performed by an experienced endoscopist, trained according to the Guidelines of the Joint Advisory Group on Gastrointestinal Endoscopy.[20] It is recommended that endoscopy reporting should be in a standard manner detailing descriptions, dimensions and locations of lesions in relation to anatomical landmarks. Failure to diagnose UGI malignancy at the patient's first endoscopy is consistently in the range of 10%, while a further 10–20% require a second gastroscopy.[21 22] The principal factors associated with the need to re-endoscope are failure to suspect malignancy and (as a consequence) failure to take adequate numbers of biopsies. In oesophageal endoscopic examination the diagnostic yield to detect high risk premalignant lesions in Barrett's reaches 100% when six or more samples are obtained using standard biopsy forceps.[23] Multiple four quadrant biopsies of the oesophagus at 2 cm intervals along its entire length have been shown to increase diagnostic accuracy and allow differentiation of high grade dysplasia from adenocarcinoma, particularly when endoscopic mucosal abnormalities are present.[24 25]

Whether or not the index endoscopy should be done on or off proton pump inhibitor (PPI) therapy is controversial. Inflammation can confound the diagnosis of dysplasia, whereas one retrospective study suggested that PPIs may mask endoscopic findings.[21] However, treatment with a PPI may also delay diagnosis or result in a misdiagnosis on first endoscopy.[21] In particular the ability of PPIs to 'heal' malignant ulcers or alter their appearance has not been fully appreciated.[26] Overall, PPIs should be stopped for the first endoscopy. For subsequent endoscopies in patients known to have Barrett's oesophagus, continuing treatment can decrease inflammation, making targeted biopsies and histological assessment easier.

If the lumen is obstructed by tumour then an ultrathin endoscope (OD, 5.3–6 mm) should be used. Oesophageal dilatation for the purposes of diagnosis should be avoided due to the high risk of perforation which may deny these patients a chance of cure.[27]

Endoscopic adjuncts

Chromoendoscopy and high resolution endoscopy have been introduced in selected centres although their role has yet to be defined. Contrast enhancing and vital dyes sprayed onto the oesophago-gastric mucosa can aid in the detection of early lesions. The most well established are Lugol's iodine for dysplastic and malignant squamous mucosa and indigo carmine for early cancer in gastric mucosa.[28 29] Acetic acid chromoendoscopy enhances detection of occult neoplasia in Barrett's.[30] Currently, these techniques are only recommended in selected patients deemed at high risk. Furthermore, with the advent of new endoscopic modalities such as narrow band imaging and autofluorescence and with the development of magnifying (zoom) and confocal endoscopes, these techniques may be superseded.[31] However it should be emphasised that there are no randomised data to indicate that these modern techniques are as good as conventional histopathology let alone suitable to replace it.[32] There is increasing interest in ultrathin nasal endoscopy and non-endoscopic approaches which have the potential to be used in the outpatient setting with increased patient acceptability.[33 34]

Higher risk groups

Individuals at increased risk of oesophago-gastric cancer on the basis of family history (tylosis) or a premalignant condition (Barrett's oesophagus, pernicious anaemia, intestinal metaplasia of the stomach or previous gastric surgery) may be considered for endoscopic monitoring. These decisions are complex and should be determined by balancing the magnitude of the benefits against the perceived clinical risks of the procedure and patient preferences. Patients with a family history of gastric cancer should be assessed to determine the risk of hereditary diffuse gastric cancer and referred for management at appropriate centres.[35] The principal condition for which endoscopic surveillance may be recommended in the UK is for diagnosed Barrett's oesophagus. Currently there are not any recommendations to screen individuals with reflux for the presence of Barrett's oesophagus in the primary care population. However, in the annual report of the Chief Medical Officer published in 2008, minimally invasive screening tests were put high on the research agenda due to the worrying increase in the incidence of oesophageal adenocarcinoma.[36] The recent report of spoge cytology to select for endoscopy is a novel and encouraging approach.[33]

STAGING

Advances in therapeutic techniques including the use of multimodality treatment regimens require accurate initial staging and assessment of treatment response. Imaging techniques should provide staging assessment according to the TNM classification. Since up to 50% of patients present with metastatic disease, initial assessment must establish the presence or absence of distant disease. Precise local staging is required to determine the depth of tumour spread in early tumours which may be amenable to endoscopic resection. In more advanced tumours accurate local staging should include depth of invasion with reference to surgical margins with clear delineation of craniocaudal and radial margins and presence and extent of lymph node metastasis to determine the likelihood of regional control.

The principal imaging modalities for staging are multidetector CT (MDCT), EUS and PET integrated with CT (PET-CT). Although MDCT has been the initial modality to exclude gross metastatic disease, all three techniques should be used in combination to provide comprehensive staging detail.

Technique

Endoscopy

Endoscopy and EMR is an essential method to stage early neoplasia. It is indicated for the assessment of areas of Barrett's with dysplasia and nodularity where invasive disease is suspected. The depth of resection is usually into the submuosa. In a comparative study Wani and colleagues found submucosa in 88% of EMR samples compared with 1% of biopsy samples, and the overall interobserver agreement for the diagnosis of neoplasia was significantly greater for EMR specimens than biopsy specimens.[37] It allows assessment not only of depth of penetration but also of degree of differentiation and vascular and lymphatic involvement. It is superior to EUS in staging early T1 cancers.[38–40]

CT scanning

MDCT images of the chest, abdomen and pelvis are acquired at fine collimation enabling multiplanar reformats to be performed with the same resolution as axial images (slice thickness should be 2.5–5 mm). The studies should be performed after intravenous contrast unless contraindicated. One litre of water can be used as an oral contrast agent. It is optimal to give ~200 ml just prior to the scan for oesophageal cancer and 400 ml for gastric cancer. Antiperistaltic agents together with gas-forming granules can be administered prior to scanning to achieve maximum

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distension, although generally sufficient distension is achieved from using water alone. Tumours in dependent areas such as at the oesophago-gastric junction can be imaged prone or in the decubitus position. The use of multiplanar reformat images in addition to axial images improves the accuracy particularly for T3 versus T4 disease, due to the ability to evaluate possible invasion of tumour into its surrounding structures in multiple planes.[41 42] MDCT also allows for volumetric analysis, so-called 'virtual endoscopy'. Some recent experimental studies in small patient cohorts have shown an additional benefit of using the virtual endoscopy images together with conventional axial images. The three-dimensional (3D) endoscopic view improves radiological detection of early tumours which manifest as shallow ulcers, not detected on the axial images.[43 44]

Endoscopic ultrasound

EUS should be performed by experienced endosonographers utilising the full range of modern radial and linear equipment.[45 46] Outcome is experience related. Centres should perform at least 100 staging examinations annually, and each centre should have at least one fully trained endosonographer. EUS examination may be limited by stricture formation. Dilatation has a high risk of perforation.[47] Options to assess strictured cancers include the blind tapered probe which improves the percentage of traversable tumours or the miniprobe in combination with guidewire placement under radiological screening.[48]

Nodal metastases are suggested by four echo pattern characteristics: (1) size >10 mm; (2) well-defined boundary; (3) homogeneously low echogenicity; and (4) rounded shape. All four may only be present in 25% of cases thus significantly reducing sensitivity.[49 50] EUS fine needle aspiration (FNA) cytology of potential nodal disease has been shown to improve accuracy. At least three passes with the EUS-guided FNA needle are recommended to maximise sensitivity.[51] Although EUS alone is not suitable for M staging, combination with FNA is an accurate and safe method for assessment of solid lesions such as adrenal or liver metastases or for aspiration of ascites.[52 53]

PET and PET-CT scanning

The combination of metabolic assessment with 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET and integrated CT provides both functional and anatomical data. The key advantage of the technique is that patient position is unchanged between each procedure and this allows for reliable co-registration of the PET and the CT data. Several technical issues remain to be evaluated such as the use of iodinated contrast media, CT technique, and optimal FDG dose and uptake period.

T staging

EMR is the preferred approach for assessing mucosal and submucosal penetration in small early (T1) cancers. EUS is more accurate for T staging in more advanced lesions because of the precise visualisation of the separate layers of the oesophageal and gastric wall. MDCT is limited for early stage disease. Similarly, studies with PET-CT have reported failure to detect early stages (T1 and T2) and poorly cellular mucinous tumours. In addition, smooth muscle activity and GORD may artefactually produce false-positive results. In gastric cancer, tumour site, size and histological type affect FDG-PET detection. Distal tumours, T1 and T2 tumours, and diffuse-type cancers show consistently low rates of detection.[54]

N staging

The assessment of nodal disease by each technique is variable according to the anatomical relationship of lymph nodes to the primary tumour. EUS (alone or in combination with CT) has a sensitivity of 91% for detecting local nodal disease.[55] Although PET-CT can identify local nodes, avid uptake by the adjacent tumour can obscure uptake by small volume metastatic nodes.

For regional and distant nodal disease, PET-CT has been shown to have a similar or better accuracy than conventional EUS-CT (sensitivity and specificity 46% and 98% vs 43% and 90%, respectively; sensitivity and specificity 77% and 90% vs 46% and 69%, respectively). Thus a combined approach with CT, EUS and PET-CT has the highest possible yield for accurately assessing nodal status.[55]

M staging

Conventional imaging with EUS and CT has a wide range of accuracy for detecting metastatic disease (sensitivity 37–46%, specificity 63–80%). The addition of PET has significantly improved detection rates (sensitivity 69–78%, specificity 82–88%), and this is particularly advantageous for identifying unsuspected metastatic disease which is present in up to 30% of patients at presentation. The American College of Surgical Oncology Group trial of PET to identify unsuspected metastatic disease has demonstrated some limitations, with 3.7% false-positive and 5% false-negative rates.[56] PET has similar limitations to CT in detecting peritoneal disease possibly due to lesion sizes of <5 mm and a low viable cancer cell to fibrosis ratio.[54] The most recent studies with PET-CT have shown superior accuracy over PET and CT performed separately, particularly in the neck, locoregional nodes and in postoperative fields. Further evaluation (including surgical excision or biopsy) of PET/CT-positive unusual nodes or single 'hot spots' is recommended because of the potential risk of false positives.

Laparoscopy

Laparoscopy is established for direct visualisation of low volume peritoneal and hepatic metastases as well as assessing local spread for operability, particularly in gastric cancer. de Graaf and colleagues have reported additional treatment information from laparoscopy in 17.1% of distal oesophageal and 17.2% of oesophago-gastric junctional tumours, as well as 28% of gastric cancers.[57] The addition of peritoneal cytology has been debated, with regard to whether positive cytology in the presence of operable gastric cancer with subserosal or serosal invasion would change surgical planning. Nath and colleagues have recently shown that patients with oesophageal and junctional cancers with positive peritoneal cytology have a poor prognosis, with a median survival of 13 (range 3.1–22.9) months.[58] The authors concluded that such patients should not proceed to radical surgery and be considered for palliative intervention.

MRI

There is no clear evidence that MRI offers any advantage over CT and EUS in the local staging of oesophageal or gastric cancer.[59 60] The majority of studies to date have used either low field strength magnets or ex vivo analysis.[61] There has been some recent development using a high resolution technique with an external surface coil for local staging of oesophageal cancer which shows promise, although the work requires substantiating in a larger clinical series.[62] MRI is also useful in the characterisation of indeterminate liver lesions detected on CT.[63 64]

Bronchoscopy

Tumours at or above the level of the carina may invade the tracheobronchial tree, and this can be assessed with bronchoscopy

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and biopsy if indicated. In experienced hands, EUS alone may be sufficiently accurate to exclude airway invasion, but if there is uncertainly a bronchoscopy should be performed.[65] This may be supplemented with endobronchial ultrasound in combination, if appropriate, with guided aspiration for cytology of mediastinal nodes.

PATHOLOGY

The RCPath and the Pathology Section of the British Society of Gastroenterology strongly advocate that there should be standardisation of reporting guidelines of all cancers.[66] Such an approach is intended to provide both the patient and clinican with prognostic information, allowing the clinician to determine the most appropriate clinical management and facilitate audit of diagnostic and therapeutic interventions.

Process

The RCPath Guidelines recommend approaches to the practical handling of biopsies and endoscopic and surgically resected specimens. Histopathologists are advised to ensure all pathological material from patients referred to the MDT is reviewed and correlated with clinical and radiological information. In addition specimens of squamous and glandular dysplasia and high grade dysaplasia and early cancer in Barett's metaplasia should be reported by two independent, named expert pathologists.[67]

Referral for review or specialist opinion

Referral for treatment

All patients referred for specialist treatment must be reviewed and discussed by the MDT. The complete diagnostic pathology report must be available and the histological and/or cytological material should be reviewed prior to, and at, the meeting. This is particularly important if there is a significant discrepancy with the clinical/radiological findings. A formal report should be issued by the reviewing pathologist to the clinician or pathologist initiating the referral. Where patients have been referred for non-surgical oncology treatment, requests for specialist biomarker studies will be coordinated between the treating oncology service, their local pathology service and the referring hospital's pathology service, as appropriate.

Referral for specialist opinion

In cases of diagnostic difficulty, referral will be made to the Lead Pathologist of the specialist MDT, although referral to other specialists within or outside the network may be appropriate in individual cases. Cases referred for individual specialist or second opinion will be dealt with by the individual pathologist and a report issued by them. Where relevant, tissue blocks should be made available to allow any further investigations that are deemed appropriate. It is strongly recommended that slides and blocks are not posted together: if they are, then there is a danger that the entire specimen is lost for ever.

All diagnostic material should be reviewed and presented at the MDT meeting so that the individual case can be discussed with full knowledge of all relevant pathological findings. External diagnoses of dysplasia, especially when further treatment is being considered (such as radical surgery, EMR, ESD or ablation therapy), should also be reviewed at an MDT meeting and the diagnosis confirmed by at least two gastrointestinal pathologists.

More unusual tumours (such as lymphoma, melanoma, endocrine tumours, small cell carcinoma or gastrointestinal stromal tumour (GIST)) should be reviewed in the course of the MDT meeting.

Data sets for reporting

The data sets have been subdivided into core and non-core data. Core data are the suggested minimum requirement for appropriate patient management, such data having been shown to be of prognostic significance. Non-core data are additional data that do not have a sufficient basis in published evidence to be a requirement, but may be of potential interest and use in patient management. The data items required for diagnostic biopsies, endoscopic resection specimens and therapeutic resections are shown in table 1. Specimen photography is invaluable in recording the macroscopic appearances of pathological specimens and aids with radiological audit. Photography should include the undissected specimen to demonstrate margins and potential defects in margins, and also the entire sliced specimen to demonstrate the quality of surgery and the extent of depth of spread of the tumour. In both oesophageal and gastric cancer, the end resection margins are also very important and should be sampled in all cases. Submucosal lymphovascular spread, in particular, can result in involvement of margins, particularly of the proximal oesophageal margin at a very considerable distance from the primary tumour. For circumferential margin assessment, there is little value in attempting to measure the distance from the tumour to the circumferential margin if there has been previous surgical dissection of the specimen for perioesophageal lymph nodes; therefore, it is recommended that all oesophagectomy specimens are left entirely in situ after surgical removal to allow the pathologist to assess circumferential resection margins accurately.

The data set items may be reported in a proforma either within or instead of the free text part of the pathology report, or recorded as a separate proforma. In general the recording of both free text report and of all items in the RCPath data sets is recommended, the latter in a structured way, either directly onto such a proforma or alternatively using the same structure on the pathology report. Trusts and MDTs should work towards recording and storing the data set items as individually categorised items in a relational database, so as to allow electronic retrieval and to facilitate the use of pathology data in clinical audit, service planning and monitoring, research and quality assurance. It is anticipated that such data recording will become a requirement as part of recommendations of the UK National Cancer Intelligence Network.[69] Laboratories should use an agreed diagnostic coding system (eg, SNOMED). All malignancies should be reported to the local Cancer Registry.

Grading conventions

Riddell-type classifications are recommended for the grading of all dysplasia in the UGI tract.[70] The Revised Vienna classification of gastrointestinal epithelial neoplasia can be used but this system has not found particular favour in the UK.[71] The WHO invasive carcinoma grade system is recommended for tumour grading.[72]

Staging conventions

The RCPath Guidelines have been based on the TNM 5th/6th editions. There were, however, discrepancies between the two editions and, as a result, the guidelines recommended TNM 6 for oesophageal cancer and TNM 5 for gastric cancer. However, pathological staging of oesophago-gastric junctional cancer was not defined. The Siewert classification was recommended, although this largely describes clinical features.[73 74] For practical purposes, the guidelines recommended that if >50% of the tumour involved the oesophagus the tumour should be classified as oesophageal, if <50% as gastric. Tumours exactly at the

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Table 1 Data set items for therapeutic resections

Biopsies	Endoscopic resections	Therapeutic resections
Tumour type	Tumour type	Specimen type
Presence of associated epithelial dysplasia when identified	Assessment of minimum depth of invasion	Length of specimen
Assessment of minimum depth of invasion, identification of submucosal invasion when this is present in the biopsy (level, not measurement)	Presence of associated epithelial dysplasia when identified	Site of tumour
	Identification of submucosal invasion when present	Macroscopic appearance of tumour
	Assessment of completeness of excision of both dysplastic and malignant components	Dimensions of tumour
	Assessment of vascular invasion	Distance to margins
		Invasive tumour type
		Invasive tumour grade of differentiation
		Character of the invasive margin that is expansile or infiltrative gastric cancer
		Serosal involvement
		Depth of invasion
		Vascular invasion
		Number of regional lymph nodes examined
		Number of involved regional lymph nodes
		Number and site(s) of distant (non-regional) lymph nodes submitted and number involved (M1)
		Distance to circumferential margin and status of this margin (in oesophageal cancer <1 mm regarded as involved). Local dissection of lymph nodes may compromise the estimation of the circumferential margin, but the distance to the remaining margin should be stated
		Status of proximal and distal margins
		Other relevant pathology (Barrett's oesophagus, background dysplasia, chronic gastritis, *Helicobacter pylori* status, etc.)
		TMN staging system, including R status
		Response to neoadjuvant therapy categorised with the Mandard criteria[68]

junction should be classified according to their histology, so squamous cell, small cell and undifferentiated carcinomas should be oesophageal and adenocarcinomas should be gastric.

In 2009 the Union for International Cancer Control in collaboration with the American Joint Committee on Cancer published TNM 7th edition which has significantly changed the staging descriptions.[75 76] The issue of oesophago-gastric junctional cancer has disappeared. Tumours including the oesophagus and within 5 cm of the oesophago-gastric junction are classified as oesophageal cancers and all others are gastric cancer. The T stage has now become consistent with T2 and T3 tumours defined for both sites; the previous T2a and T2b subgroups in gastric cancer have been removed. Nodal staging for both oesophageal and gastric cancers has been unfied with N0, N1, N2 and N3 subgroups. This revision has created significant concerns particularly as historical comparisons will now be more difficult. The RCPath has recently recommended that TNM 7 should be adopted in the UK. This will take some time to implement and the effect on practice is likely to evolve. The current consensus is that TNM 7 will become the standard for staging, but the clinical classification will continue with the Siewert system as this will influence the selection of surgical procedure. The effect on clinical trials, however, is more difficult to predict as the current large trials are based on TNM 5 and 6 criteria.

PRETREATMENT ASSESSMENT

The aim of preoperative co-morbidity assessment is to provide the opportunity of optimising the patient's physiological status to undergo potentially curative treatment (including surgery or definitive chemoradiotherapy). There are a number of established risk predictors, but there is a lack of consensus on the selection criteria for patients undergoing gastric and oesophageal resection or radical chemoradiotherapy or radiotherapy alone.

Exercise testing

Poor exercise tolerance correlates with an increased risk of perioperative complications which are independent of age and other patient characteristics. Although exercise capacity is a subjective estimation it can be a useful measure of functional cardiorespiratory reserve. Any patient who remains asymptomatic after climbing several flights of stairs, walking up a steep hill, running a short distance, cycling, swimming or performing heavy physical activity should tolerate UGI surgery. However, it is important to appreciate that an apparent ability to perform these activities does not exclude cardiorespiratory disease and, indeed, this is a major criticism of exercise testing performed in the absence of cardiopulmonary monitoring.[77] Malnourished patients will also exhibit a reduced exercise tolerance. The true value of preoperative exercise testing currently remains debatable. In the absence of accepted evidence-based data, and the lack of an agreed protocol, exercise testing for UGI cancer surgery patients remains an area worthy of consideration and evaluation but should not be used as a sole criterion for denying someone an operation.

Stair climbing

Patients with poor exercise tolerance, defined as an inability to climb two flights of stairs without stopping, have more co-morbidity, higher ASA (American Society of Anesthesiologists) scores and postoperative complications. Although this test is a subjective assessment, there is some evidence that where this is not possible there is an almost 90% chance of developing

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postoperative cardiorespiratory complications.[78 79] Desaturation during exercises equivalent to climbing three flights of stairs, suggesting an inability to meet the increased metabolic demands of exercise, appears to have some predictive power as regards postoperative complications in patients undergoing lung reduction surgery. Exercise-induced hypotension, possibly indicating ventricular impairment secondary to coronary artery disease, is an ominous sign and must be further investigated.[77]

Cardiopulmonary exercise (CPX) testing

CPX testing is a dynamic non-invasive objective test that evaluates the ability of the cardiorespiratory system to adapt to a sudden increase in oxygen demand.[79] The ramped exercise test is performed on a cycle ergometer with ECG monitoring and analysis of expired carbon dioxide and oxygen consumption, the latter being directly related to oxygen delivery and a linear function of cardiac output when exercising. A 24% incidence of previously undetected and 'silent' ischaemic heart disease has been reported during CPX testing.[79]

With increasing exercise, oxygen consumption will eventually exceed oxygen delivery. Aerobic metabolism becomes inadequate to meet the metabolic demands, and blood lactate rises, reflecting supplementary anaerobic metabolism. The value for oxygen consumption at this point is known as the anaerobic threshold (AT), expressed as ml/kg/min. A greater mortality has been reported in patients with an AT <11 ml/kg/min undergoing major abdominal surgery, the risk being compounded by the presence of ischaemic heart disease.[79]

Advocates of CPX testing claim the results can be used to stratify operative risk, identify those who will most benefit from presurgery optimisation and facilitate anaesthetic and postoperative care. It may be particularly useful in those patients in the intermediate risk group of the ACC/AHA (American College of Cardiology/American Heart Association) preoperative cardiac evaluation guidelines. A valued reliable preoperative assessment of risk is crucial in this group, but can be fraught with difficulties.[79]

In a study of 91 patients who had undergone transthoracic oesophagectomy, maximum oxygen uptake during exercise correlated well with postoperative cardiopulmonary complications.[80] The authors concluded that transthoracic oesophagectomy can safely be performed on patients with a maximum oxygen uptake of at least 800 ml/min/m^2. This conclusion has been disputed in a recent study of 78 consecutive patients who had CPX testing prior to oesophagectomy, where CPX testing was found to be only of limited value in predicting postoperative cardiopulmonary morbidity.[81] Limitations of CPX testing can occur in patients with reduced lower limb function related to osteoarthritis or limb dysfunction.

Shuttle walk test

A simpler and more viable alternative to CPX testing is incremental and progressive shuttle walk testing (SWT).[82] SWT endurance appears to correlate well with oxygen utilisation seen in CPX. In a study of 51 patients undergoing oesophageal resection, preoperative SWT was a sensitive indicator of 30 day operative mortality. Although the causes of death or complications were not recorded, no patient who walked >350 m on SWT died.[83] The authors suggest that the inability to maintain adequate oxygen delivery, as reflected by an exercise tolerance of <350 m at SWT, may impair wound healing and increase anastomotic failure.

Patients with musculoskeletal disease and morbid obesity may be unable to complete any form of dynamic exercise testing. In such circumstances, upper limb ergometry, pharmacologically induced myocardial stress testing monitored by thallium imaging or ECHO cardiography may be an alternative. Meticulous history taking, clinical examination, baseline investigations and exercise testing will help identify those patients who need further non-invasive or invasive investigation such as echocardiography, myocardial stress testing, imaging and angiography.[84] Only after thorough assessment can the appropriateness of the planned anaesthesia and surgery be determined.

Nutritional status

Preoperative malnutrition is associated with higher rates of morbidity, including infection, delayed wound healing and pulmonary complications (including adult respiratory distress syndrome with associated increased mortality).[85] Malnutrition is common and may be related to dysphagia, disease cachexia or neoadjuvant chemotherapy. Assessment of nutritional status at presentation and before surgery is therefore recommended. Malnutrition is defined as:

- A BMI of <18.5 kg/m^2
- Unintentional weight loss >10% within the last 3–6 months
- A BMI <20 kg/m^2 and unintentional weight loss >5% within the last 3–6 months.

Additional biochemical measures can contribute to the assessment of nutritional status, although serum albumin which reflects an acute phase response is not a reliable marker of malnutrition.[86]

PERIOPERATIVE OPTIMISATION

Appropriately directed perioperative care is associated with an improved surgical outcome in those with recognised risk predictors. Establishing that current treatment for co-existing cardiorespiratory disease is optimal is essential prior to any additional interventions directed towards optimising preoperative status.

β-Blockade

There has been much interest in adrenergic β-blockade prior to major surgery as a means of improving ischaemic ventricular dysfunction.[87] Current ACC/AHA guidelines suggest that β-blockers should be considered in all patients with an identifiable cardiac risk as defined by the presence of more than one clinical risk factor.[86 88] For the treatment to be efficacious, patients should be optimally β-blocked in the weeks preceding elective surgery and continued throughout the immediate postoperative period. Although no particular β-blocker has been identified as preferable, long-acting β-blockers initiated before surgery were thought to be superior to shorter acting drugs.[88]

The protective mechanism of β-blockers is unclear, the control of heart rate being only part of the explanation. In contrast, recent critical expert re-evaluation of perioperative β-blockade has questioned the validity of some of the evidence that β-blockers are indeed cardioprotective.[89] Adverse effects can be associated with β-bockade, especially the non-selective β-blockers. Vagal responses to surgery and anaesthesia can be exacerbated by concomitant β-blockade, and responses to sympathomimetic inotropes may be altered.

Statins

There is growing interest in statins as a pre-emptive intervention treatment in the preoperative period in patients with ischaemic heart disease or hypercholesterolaemia. A meta-analysis of postoperative outcome following cardiac, vascular and non-cardiac surgery demonstrated a significant reduction in early

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postoperative mortality in patients taking long-term statins.[90] An alternative review, however, felt that the evidence for the routine perioperative use of statins to reduce cardiovascular risk was currently lacking.[91] To date no specific studies evaluating perioperative statin treatment and postoperative outcome following gastric or oesophageal surgery have been reported. Current ACC/AHA guidelines on perioperative cardiovascular care recommend that patients should continue statin treatment throughout the operative period.[84] Until further prospective studies can clarify the true value of statins in the perioperative period, their continuation is at the discretion of the attending clinician.

Goal-directed haemodynamic preoptimisation

The normal physiological response to surgery is to increase oxygen delivery by an increase in cardiac output. Shoemaker and colleagues showed that patients who incurred an oxygen debt as a consequence of limited cardiorespiratory reserve incurred more postoperative morbidity and mortality.[92] Non-survivors tended to have the greatest and most persistent oxygen debt. Goal-directed optimisation aims to attain predetermined target physiological parameters that are known to correlate with a favourable outcome. With the aid of invasive monitoring, using crystalloid, colloid, blood, inotropes and oxygen, heart rate, stroke volume, haemoglobin and oxygen saturation can be manipulated.

Following a period of preoptimisation, a reduction in mortality and length of hospital stay was reported, with preoperative fluid loading considered the most important factor.[93] A positive effect on surgical outcome after oesophagectomy has been demonstrated with judicious fluid administration.[94]

When fluid loading alone fails to attain the predetermined physiological targets, inotropes such as dopexamine, dobutamine and epinephrine have been used. However, they can alter regional blood flow, cause tissue hypoxia and increase myocardial oxygen demand, provoking ischaemia. An adequate cardiac output is not necessarily synonymous with good regional or anastomotic blood flow. Goal-directed preoptimisation may be beneficial in appropriately selected high risk patients. It has been advocated that only those patients undergoing surgery for which mortality exceeds 20% and those identified as high risk during risk stratification should be considered.

Nutritional support

Patients who are identified as malnourished prior to surgery should be considered for preoperative nutritional support for 10–14 days.[95] Liquid nutritional products containing immunonutrients, namely arginine, omega-3 fatty acids and nucleotides, have been used in preoperative and postoperative patients undergoing surgery for UGI malignancies. Some, but not all, RCTs have demonstrated a reduction in postoperative infective complications in both malnourished and normally nourished patients when used for 5–7 days preoperatively.[96–98] Studies in malnourished patients included use of both preoperative and postoperative immunonutrition and it may be that this group of patients require immunonutrition both preoperatively and postoperatively to gain benefit. Its use may also reduce length of hospital stay.[98–100]

Postoperative feeding via the jejunal route is routine in some centres, and this may improve nutritional status, although evidence to show improved clinical outcomes compared with standard care is currently lacking. It is recommended that nutritional support should be provided for all patients who are malnourished or at risk of malnutrition and have an inadequate oral intake defined as having eaten little or nothing for >5 days and/or likely to eat little or nothing for the next 5 days or longer. Preferably this should be given via the gastrointestinal tract if it is functioning and adequate access can be obtained.

Thromboembolic disease

Venous thromboembolism (VTE) is a not infrequent co-morbidity in patients with oesophageal or gastric cancer. This is not only because of the higher risk of VTE for patients with malignancy but also because VTE is associated with some chemotherapy regimens. All patients considered for surgery should be offered VTE prophylaxis according to NICE guidance.[101] Patients who have recently sustained a VTE should be considered for placement of temporary caval filters prior to radical surgery.

TREATMENT

Endoscopic therapy

Endoscopic therapy has become an integral part of the multidisciplinary management of oesophageal and gastric cancer. The UK NICE guidance recommends that such procedures need to be carefully audited in high volume tertiary referral centres with access to an oesophageal and gastric cancer surgeon, should be performed by appropriately trained staff, and patient care must be managed through an MDT.[102 103]

EMR and ESD, PDT, mucosal ablation using lasers (photothermal), electrocoagulation, APC and radiofrequency ablation (RFA) (thermal) have all been employed to remove dysplasia and early cancer. Most techniques are now being used in combination to eradicate local disease and address any field change abnormality.[104–106] It is important to emphasise that patients must have reversal of the underlying abnormality with reflux control and *H pylori* eradication and have repeat endoscopic surveillance to detect metachronous or recurrent tumours.

Oesophageal cancer and high grade dysplasia

Pathology

The pathology of early cancer of the oesophagus varies with histological subtype. In one review, Stein and colleagues reported that submucosal infiltration was more frequent in T1 squamous cancers (80.5%) than in T1 adenocarcinomas (55.4%).[107] The risk of lymph node involvement is also greater in squamous cell carcinoma. An analysis of 1690 lesions has reported the risk of lymph node metastases with early oesophageal squamous carcinomas as being 19% for lesions invading the muscularis mucosa and 44% for lesions invading deeper than the superficial one-third of the submucosa.[108] In contrast, the risk of nodal disease in adenocarcinoma limited to the muscularis mucosa is negligible. In submucosal infiltration of adenocarcinoma the risk of lymph node spread reflects the depth of invasion. Once penetration into the superficial third (sm1) has occurred, the risk is 0–8% and once through into sm2 and sm3 it rises to at least 26%.[38]

Treatment

Endoscopic resection

Data from the from the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute (USA) examined patients with stage 0 (Tis N0 M0) and stage 1 (T1 N0 M0) early adenocarcinoma of the oesophagus. This demonstrated no significant difference in survival of patients treated with endoscopic therapy compared with those having a radical surgical resection.[109 110]

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Endoscopic resection is indicated for early cancer (T1mN0), moderately and well differentiated cancers and mucosal dysplasia.[111] There are now consistent reports indicating a 5 year disease free survival (DFS) of 95% and a low morbidity rate.[112–114] Similarly, early mucosal Barrett's cancer and dysplasia can be safely eradicated.[105] The use of a single and purely localised therapy can result in the development of metachronous cancer in up to 30% of patients. The risk of recurrence can be reduced to 16% by ablation of the remaining Barrett's epithelium with PDT, with a complete long-term control of 96% at a median of 5 years follow-up.[105] Similarly eradication of the Barrett's segment with RFA improves local control particularly for flat areas of dysplasia and reduces the risk of malignant degeneration.[115 116]

Comparative studies (non-randomised and retrospective) of surgery and endoscopic ablation therapy for dysplasia and early cancer are misleading because of selection bias.[110 117 118] Patients selected for endotherapy are older with earlier tumours and small segments of Barrett's oesophagus. Overall survival (OS) and cancer-related mortality seem to be very similar (>90%), with significantly fewer complications associated with endotherapy.[110 117 118] Circumferential EMR is associated with stricture formation but can be used to destroy the field change in Barrett's oesophagus and eradication of mucosal cancer.[119 120] Well-designed and conducted RCTs comparing the effectiveness and cost-effectiveness of endoscopic therapy with surgical resection are urgently required.

Photodynamic therapy

Treatment of early cancer and high grade dysplasia in Barrett's oesophagus, squamous cell dysplasia/cancer and adenocarcinoma of the oesophagus with PDT has resulted in prolonged survival which is comparable with surgery.[118 121–123] There are large case series of PDT for the treatment of Tis, T1 early and some T2 squamous cell and adenocarcinoma, with a complete response reported of 40–93% with follow-up of 4–47 months.[118 122–125] The main complications have been skin photosensitivity and stricture formation, with perforation occurring in 4–34% of patients.

In a randomised trial using PDT to eradicate high grade dysplasia, patients (208) were randomised 2:1 to endoscopic PDT with omeprazole or received omeprazole (control) only.[126] There was a significant difference ($p<0.0001$) for PDT (106/138=77%) compared with control (27/70=39%) in complete ablation of high grade dysplasia. The occurrence of adenocarcinoma in the photodynamic group was significantly lower ($p<0.006$). The response remains robust at 5 year follow-up.[126] PDT is the most cost-effective solution for the management of high grade dysplasia in Barrett's oesophagus when compared with surveillance and radical surgery.[127 128]

Thermal ablation

Laser, APC, electrocoagulation, cryotherapy, RFA

These methods are used to eradicate field change in Barrett's oesophagus, destroy any occult synchronous cancers and prevent the development of metachronous lesions after EMR of all macroscopic lesions. The optimal method of ablation has been much debated.[129]

Since APC is in widespread use, many single device and comparative studies have compared this with other methods. Current evidence shows that complete eradication rates vary from 38% to 99%.[130–133] It is important to have profound acid suppression.[134] Complications of haemorrhage, perforation and stricture do occur (10%). An RCT comparing APC against endoscopic surveillance following antireflux surgery demonstrated significant reversal of Barrett's (follow-up 12 months) following APC.[135]

Randomised studies have compared APC with PDT. The results vary, with no significant difference between ALA (5-aminolaevulinic acid)-PDT and APC, and others finding APC simpler and more effective.[136 137] Photofrin PDT was more effective than APC in eradicating, dysplasia although not significantly so (12 months follow-up). The complication rate was similar but PDT was more costly.[138] Multipolar electrocoagulation requires fewer treatment sessions than APC, with an ablation rate of 88% compared with 81% (APC).[139] None of these trials was able to assess progression to cancer.

RFA has proved an effective method for eradication of preneoplastic Barrett's epithelium.[140 141] Recent randomised data compared RFA with sham treatment, and have demonstrated the short-term effectiveness of RFA. Eradication of dysplasia and prevention of progression to cancer in patients with dysplastic Barrett's oesophagus was achieved using RFA. At 12 months high grade dysplasia was eradicated in 81%, with only 2.4% progressing to cancer (RFA) compared with 19.0% eradication and a 19.0% progression to cancer (sham treatment). Strictures developed in 6%, bleeding in 1%, and 2% of patients needed admission to hospital for pain.[116] Long-term follow-up and further research to establish the role of this intervention are still needed. The optimal management of high grade dysplasia in Barrett's is currently being assessed by an international consensus task force (BArrett's Dysplasia and CAncer Task force; BAD CAT) and is due to report at the end of 2011.

Gastric cancer

In gastric adenocarcinoma mucosal disease is associated with a 0–3% incidence of lymph node metastases, rising to 20% for deep submucosal disease.[142 143]

Studies show that after 30–39 months, two-thirds of patients with EGC (Japanese criteria) and high grade dysplasia (non-invasive neoplasia; Western criteria) will progress to an invasive cancer.[144 145] Long-term survival is now consistently being reported following endoscopic resection of EGC.[146] Thus, the criteria for endoscopic therapy (EMR and ESD) have been extended by the Japanese Gastric Cancer Association from mucosal cancer, well differentiated non-ulcerated small lesion (<2 cm), to any size (elevated), ulcerated (<3 cm) and includes undifferentiated subtype.[106]

SURGERY

There is a strong relationship between lower hospital mortality and increasing surgeon and institutional patient volumes.[147 148] Large volume units consistently report hospital mortalities well below 10%. In the National Oesophago-Gastric Cancer Audit during October 2007–September 2008, 1109 and 747 patients underwent curative resection for oesophageal and gastric cancer, respectively. The hospital mortality was 5.0% (95% CI 3.8% to 6.4%) for oesophagectomy and 6.7% (95% CI 5.0% to 8.7%) for gastrectomy.[3] The proportion of patients undergoing radical curative resection has fallen. In 1998 overall resection rates were 28% (oesophageal 14%, oesophago-gastric junctional 33% and gastric 31%) decreasing to 20% in 2005 (oesophageal 10%, oesophago-gastric junctional 24% and gastric 23%). These changes are likely to reflect service reconfiguration following implementation of IOG and better staging and MDT working.[1 149]

The benefit of surgeon and surgical team volume is less well defined. However, surgeon competence does seem to plateau

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with increasing experience.[150] A prospective audit of the learning curve for D2 gastrectomy reported that such a plateau was reached after 15–25 procedures.[151] A number of factors have influenced surgeon experience including reduction in resection rates, centralisation with a trend towards team working, and reduced working hours in the context of providing a comprehensive UGI surgical service. It would seem therefore that an individual surgeon should be undertaking a minimum of 20 oesophageal and gastric resections annually, either individually or in conjunction with a consultant colleague. The National Oesophago-Gastric Cancer Audit has clearly shown the standards that have been reached, and an individual's practice should be audited against these benchmarked standards. AUGIS has recommended that an ideal oesophago-gastric unit should consist of 4–6 surgeons each carrying out a minimum of 15–20 resections per year serving a population of 1–2 million.[152]

Oesophageal surgery

The histological tumour type, its location, the extent of the proposed lymphadenectomy, patient factors and the experience of the surgeon should determine the operative approach. In Western patients there is little evidence that any particular approach is superior to another in terms of OS. A large and well-designed randomised trial in patients with lower oesophageal and type I and II oesophago-gastric junctional tumours compared transhiatal with transthoracic resection and extended lymphadenectomy.[153 154] Operative morbidity rates were significantly lower in the transhiatal group, but in-hospital mortality rates were similar. Transhiatal surgery was associated with a survival benefit, although this did not reach standard levels of statistical significance (p=0.06). Subgroup analysis showed a slight advantage for transthoracic resection for type I tumours and those which were node positive.[154] In the early postoperative months patients undergoing transhiatal surgery reported fewer problems with activity levels and pain than those undergoing more extensive resection. By 12 months, however, scores were similar in both groups. This information may be important to patients when selecting surgical procedures.[155]

Studies claiming benefits for a particular approach usually hide multiple confounders, of which the potential for stage migration as a result of inadequate lymphadectomy is usually important.[154 156] In an era of increasing use of neoadjuvant therapies where specific treatments are increasingly stage dependent, the surgeon should avoid carrying out an operation that is likely to underestimate the extent of disease or leave disease behind. Indeed, prospective longitudinal and population-based studies with a comprehensive evaluation of HRQL have shown that oesophagectomy has an immediate negative impact on all aspects of HRQL, and there is limited slow recovery.[157–159] Patients surviving at least 3 years report persistent problems with reflux, dyspnoea and reduced physical activity, and those not living beyond 12 months and likely to have undergone non-curative surgery do not regain preoperative HRQL levels.[160 161]

For squamous carcinoma, adequate lymphadenectomy in the mediastinum and abdomen seems logical as most Western patients have middle or upper third tumours. For this reason two- and three-phase operations are generally advocated. Transhiatal surgery seems illogical on the grounds that mediastinal lymphadectomy is likely to be compromised. This latter operation seems most suited to patients with early stage tumours thought to be node negative.

For adenocarcinomas, most surgeons accept the need for an adequate abdominal lymphadenectomy as the predominant route of lymphatic spread in lower third tumours is in a caudal direction. The extent of mediastinal lymphadenectomy, particularly in the upper half of the mediastinum, remains unclear. Experience from Munich has shown in type II oesophago-gastric junctional tumours that the pattern of lymph node involvement is mediastinal (2.1%), paraoesophageal (15.6%) and intra-abdominal (56–72%).[73] The most widely practised operation is the two-phase Ivor Lewis operation with a laparotomy followed by a right thoracic approach with the anastomosis high in the chest. Some surgeons favour a third stage with a cervical incision to create the anastomosis at this level. This may be an important consideration to gain adequate clearance in proximal tumours. Transhiatal surgery again seems best suited to early stage disease including multifocal high grade dysplasia in patients with very long Barrett's segments. A small group of patients who would not withstand thoracotomy may tolerate a transhiatal approach.

There is a growing interest in the use of minimal access techniques to replace conventional open surgery. Prospective cohort studies have shown that clinical outcomes with complete minimally invasive oesophagectomy can be achieved with good short-term outcomes.[162 163] Early experience has shown that lymph node yield from laparoscopic lymphadenectomy is similar to that obtained at open surgery.[164 165] However, there are specific complications with associated significant morbidity and mortality such as gastric tube necrosis (incidence up to 13%) which need better understanding and resolution. In all these studies the impact on gastric tube necrosis on postoperative quality of life is severe because of the necessity to form a cervical oesophagostomy. A prospective cohort study using validated measures of HRQL shows that following minimal access oesophagectomy the impact on HRQL may be less severe than standard open surgery.[166] However, there is insufficient robust evidence to reach meaningful conclusions of the impact of minimal access surgery for oesophageal cancer on HRQL, postoperative clinical outcomes and long-term survival. Consensus guidelines have been produced by AUGIS which recommends a pragmatic approach for the development of minimal access surgery for oesophageal and gastric cancer resection and should be used for learning curve, audit and research purposes.[167] It is also recommended that these new techniques are carried out by specialist teams with appropriate mentorship and training. However, only data from well-designed and conducted RCTs will be able to demonstrate the effectiveness and cost-effectiveness of minimal access as an alternative to open surgery.

Gastric surgery

The aim of surgery for gastric cancer is to excise the primary lesion with clear longitudinal and circumferential margins. The type of resection is determined by the position and preoperative stage of the cancer and the planned lymphadenectomy. In EGC which is not suitable for endoscopic resection (see above) proximal or distal partial resection is appropriate with limited lymphadenectomy. Japanese data have demonstrated that resection of the N1 tier of nodes together with the left gastric (station 7) and anterior hepatic nodes (station 8a) (D1 α) for mucosal disease and of the N1 tier with left gastric, anterior hepatic and coeliac axis nodes (station 9) (D1 β) for submucosal disease can achieve the same outcome as D2 lymphadenectomy.

The approach to cardia, subcardia and some type II oesophago-gastric junctional cancers can be extended total gastrectomy or oesophago-gastrectomy. The aim is to ensure adequate local clearance, appropriate lymphadenectomy and an uncomplicated anastomosis with low morbidity. Barbour and colleagues have reported that an ex vivo proximal margin of

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>3.8 cm of normal oesophagus (which equates to 5 cm in vivo) is associated with a minimal risk of anastomotic recurrence and is an independent predictor of survival.[168] The role of intraoperative histological examination of the proximal resection margin is mandatory in this situation. The distal margin is also a potential risk in oesophago-gastrectomy as some tumours infiltrate into the gastric fundus. Lymphadenectomy should include a formal dissection of D2 and posterior mediastinal, perioesophageal nodes. A randomised comparison of transhiatal and left thoracoabdominal extended total gastrectomy has shown superior outcome for the transhiatal group.[169] The authors postulated that this reflected the greater physiological insult associated with thoracotomy. Thus, for these tumours, a transhiatal, extended total gastrectomy should be considered with an oesophago-gastrectomy the alternative if an adequate proximal margin cannot be achieved. Non-randomised comparative HRQL data add further support for this approach.[170]

Japanese experience has clearly shown that excision of the primary lesion together with the omenta and first two tiers of lymph nodes (N1 and N2) that drain the affected area of the stomach can cure patients even in the presence of lymph node metastases—D2 or systematic lymphadenectomy. In the West, two RCTs have shown little initial difference between D1 and D2 lymphadenectomy.[134 171 172] Long-term follow-up in a Dutch trial has recently been reported, showing better cancer-related survival after D2.[173] Smaller series from specialised European centres have shown equivalent results to the Far East, with operative mortality rates well under 5% with corresponding improvements in survival.[174–176] There is emphasis on the greater expertise of the surgeon with avoidance of pancreatic and splenic resection unless specifically indicated. In addition, such expertise is reflected in the management of complications, which is important in maintaining a low operative mortality rate.[177]

Much of the stage-specific improvement in survival after D2 resection is likely to be a result of better pathological staging (stage migration factor), particularly stages II and IIIa. Staging is dependent on TNM criteria, and a minimum of 15 lymph nodes should be resected and examined histologically for reliable staging.[74] It should be noted that in the Dutch trial 20% of the D2 group with N2 nodes were still alive at 11 years.[177] Series from both Japan and the West show that a significant proportion of patients with N2 disease survive for >5 years after a D2 resection—it is unlikely that they would survive as long after a lesser lymphadenectomy.

The role of extended lymphadenectomy in which nodes beyond the second tier are resected (eg, nodes in the hepatoduodenal ligament) has been extensively studied. In a retrospective comparison, Robertson and colleagues reported no advantage of D3 over D2.[178] In a recent prospective randomised trial, Wu and colleagues have reported an improved OS with D3 compared with D1.[179] Two multicentre randomised trials in Japan comparing D2 and D4 lymphadenectomy for advanced cancer have recently reported their results.[180 181] Both trials concluded that a D4 resection did not improve survival but did increase operation-related risks. The future trend will be towards node resections that are tailored to the preoperative and operative staging of each case and to the age and fitness of the patient.[182 183]

Translating Japanese experience and recommendations to Western practice has not been without problem. As a result, in the recently revised Japanese Rules, the description of D2 dissection has been related to the extent of gastrectomy. In a D1 total gastrectomy, stations 1, 2, 3, 4, 5, 6 and 7 should be resected and in a D2 stations 8a, 9, 10, 11 and 12 are added. In a D1 subtotal gastrectomy, stations 1, 3, 4, 5, 6 and 7 are removed and in a D2 stations 8a, 9, 11p and 12a are added (T Sano, personal communication). It is hoped that this will facilitate a more standard approach to gastric cancer surgery and allow greater ease of comparing outcome across centres. The International Gastric Cancer Association has taken a consensus view to implement a standard data set worldwide for data collection and audit.

There has been increasing interest in the potential for laparoscopic resection of gastric cancer, with the procedures being either totally laparoscopic or more usually laparoscopic assisted. Studies have shown the safety of the laparoscopic procedures and confirm that a D2 lymphadenectomy can be performed to the same standard.[184 185] Most published studies are from Asia and largely comprise patients with T1 or T2 cancers. A meta-analysis of open versus laparoscopic-assisted distal gastrectomy (LADG) yielded only a small number of suitable RCTs with small sample sizes and limited follow-up. There were no differences between the groups except for a longer operating time and a reduced nodal yield in LADG.[186] There was a trend to faster postoperative recovery and discharge after LADG. It is likely that the laparoscopic procedures will continue to be developed but, as with oesophageal surgery, it is important that the lessons learnt during the development of safe open gastric cancer surgery should not be forgotten.

There is a lack of multicentre randomised trials in gastric cancer with comprehensive patient-completed assessments of HRQL. In a randomised comparison of D1 or D3 lymphadenectomy, questionnaires administered by a nurse were used to assess HRQL and it was reported that both groups had similar HRQL.[187] Another randomised trial of laparoscopy-assisted or open distal gastrectomy in EGC, also using administered questionnaires, showed HRQL advantages to minimal access surgery.[188] The risk of observer bias in these trials, however, is high because non-blinded observers and not the patients themselves performed the assessments. This is a critical design feature of conducting trials with HRQL outcomes. Prospective patient-reported outcomes evaluating the impact of gastrectomy on HRQL show that there is a marked HRQL deterioration after surgery, and total gastrectomy appears to have greater long-term HRQL deficit than subtotal surgery.[189 190]

NEOADJUVANT, PERIOPERATIVE (NEOADJUVANT AND ADJUVANT) AND ADJUVANT THERAPY

Oesophageal cancer

Historically, the majority of trials and meta-analyses evaluating combined modality treatment regimens in the treatment of oesophageal cancer have included squamous cell, adeno- and undifferentiated carcinomas, and tumours located in the proximal, mid and lower oesophagus as well as oesophago-gastric junctional tumours. These recommendations describe the current rationale for treatment strategies based on the main histological subtypes and tumour location.

Preoperative radiotherapy

A meta-analysis of preoperative radiotherapy for patients with resectable oesophageal carcinoma (any histological subtype) demonstrated that there was a 3–4% absolute improvement in OS (HR 0.89; 95% CI 0.78 to 1.01; p=0.062).[191] Preoperative radiotherapy is therefore not recommended for potentially resectable oesophageal squamous cell or adenocarcinoma.

Preoperative chemoradiation

Preoperative chemoradiation followed by surgery is superior to surgery alone, as demonstrated in a meta-analysis of 10 RCTs

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comparing the two strategies.[192] The HR for all-cause mortality was 0.81 (95% CI 0.70 to 0.93; p=0.002), corresponding to a 13% absolute difference in survival at 2 years. A significant benefit favouring preoperative chemoradiation over surgery alone was observed in oesophageal cancer of both squamous cell carcinoma and adenocarcinoma histological subtypes. There have been two further phase III trials comparing chemoradiation with surgery alone in patients with resectable oesophageal or oesophago-gastric junctional cancer. In the Dutch trial, paclitaxel and carboplatin were given with radiotherapy.[193] The median survival for the combined therapy group was 49 months compared with 26 months for the surgery-alone arm. The majority of patients (74%) had distal oesophageal tumours and ~12% had oesophago-gastric junctional tumours. In the subgroup analysis, the beneficial effect was more pronounced in patients with squamous cell carcinoma (HR 0.34; 95% CI 0.17 to 0.65) compared with adenocarcinoma (HR 0.82; 95% CI 0.58 to 1.16). In the FFCD 9901 trial, patients were randomised to combination 5-FU/cisplatin and radiotherapy.[194] The trial included 195 patients with localised stage I and II oesophageal squamous cell carcinoma (70%) and adenocarcinoma (29%). It was stopped early as there was no advantage to the combination regimen. In addition the operative mortality was significantly greater at 7.3% in those treated with chemoradiotherapy. The authors concluded that triple modality therapy was not indicated for such early stage oesophageal cancers.

Preoperative chemoradiation alone and preoperative chemotherapy have not been directly compared in the context of a phase III RCT. A phase III RCT has been conducted comparing preoperative chemotherapy with preoperative chemotherapy and chemoradiation in locally advanced lower oesophageal and gastric cardia adenocarcinoma. This study closed early due to poor accrual. A trend towards improved survival in the chemotherapy plus chemoradiation arm was reported; however, this was associated with higher perioperative morbidity.[195]

There is a lack of assessment of HRQL in the RCTs comparing preoperative chemoradiation followed by surgery with surgery alone. Prospective series evaluating HRQL during chemoradiation and surgery show a deterioration of HRQL during preoperative treatment that recovers before surgery. After oesophagectomy there is a dramatic reduction in all aspects of HRQL, but no evidence that undergoing preoperative chemoradiation delays postoperative recovery of HRQL.[196 197]

Definitive chemoradiation

Chemoradiation results in superior disease control and survival outcomes compared with radiation alone, but is associated with greater toxicity as seen in a review of 19 RCTs.[198] There are few trials directly comparing definitive chemoradiation with surgery alone. A Chinese study of 80 patients with squamous cell carcinoma randomised to surgery or chemoradiation failed to show superiority of either strategy in terms of early DFS or OS.[199] This trial was powered to show superiority of one treatment over another, but failed to report what magnitude of difference was considered superior. There is also a small Swedish study of 91 patients with either squamous cell carcinoma or adenocarcinoma of the oesophagus (50/50) that did not find any differences in treatment outcomes and equivalent survival.[200]

Adding surgery to chemoradiation for squamous cell carcinoma can improve local control rates compared with chemoradiation alone, but combined-modality therapy has not been shown to improve survival. A European study of 172 patients with squamous cell carcinoma randomised to induction chemotherapy followed by chemoradiotherapy (40 Gy) and surgery, or induction chemotherapy followed by chemoradiotherapy (at least 65 Gy) reported equivalent OS, but better local progression-free survival in the surgery arm.[201] The addition of surgery also significantly increased treatment-related morbidity (12.8% vs 3.5%; p=0.03). A second European study, the French FFCD 9102 trial, recruited 444 patients with potentially resectable oesophageal cancer of predominantly squamous cell carcinoma subtype (90%).[202] After induction chemoradiation, responding patients were randomised to further chemoradiation or surgery. Median OS was 19.3 months for patients randomised to further chemoradiation and 17.7 months for those randomised to surgery. Again toxicity was higher with combined-modality therapy. The study met its primary end point of non-inferiority for 2 year survival (p=0.03). Both the European studies were equivalence studies powered to determine whether the two treatments could be considered equivalent in terms of survival at 2 years. Equivalence was defined as a difference of <10% and 15%. It is questionable for a cancer with such a low survival rate that such differences would be deemed clinically important. The French trial included an observer-assessed measure of HRQL.[202 203] Participants randomised to surgery reported worse HRQL 3 months after treatment, but similar scores in both arms were reported at 2 years. In this trial the HRQL assessment was performed by a non-blinded observer, introducing the possibility of bias. One non-randomised prospective series comparing HRQL between patients selected for definitive chemoradiation versus chemoradiation and surgery showed a similar pattern.[204] In the first few months after treatment, HRQL was more severely comprised following a surgical than a non-surgical approach, but at 1 year scores were similar in both groups.

In localised squamous cell carcinoma of the oesophagus, although definitive chemoradiation is a current recommended standard of care, there is a lack of evidence to support either a surgical or a non-surgical approach. The recent UK National Audit shows that the disease is treated by both approaches.[3] Surgery should be considered in those treated with chemoradiation who at the end of treatment have histologically confirmed residual disease. A feasibility RCT is being set up to examine whether it is possible to effectively recruit into a trial comparing these treatment options. Ongoing clinical trials, such as SCOPE-1, are evaluating the additional effect of biological agents to treatment regimens, but trials with both clinical and HQRL outcomes comparing chemoradiation with combination treatments including surgery are still needed.

For patients with localised oesophageal adenocarcinoma deemed unsuitable for surgery, definitive chemoradiation is a valid treatment option,[205] with consideration given to participation in relevant clinical trials.

Salvage surgery after definitive chemoradiation

Local recurrence after primary treatment with definitive chemoradiotherapy may occur in 10–30% of patients within the first year. In this situation, attempted salvage curative treatment with oesophagectomy may be an option, but careful consideration by a specialist MDT is required in making this high risk judgement. Repeat staging investigations including PET-CT and EUS are recommended. Surgery should be undertaken by a specialist team, and a recent review summarising earlier studies showed an increased in-hospital mortality rate after salvage surgery (up to 17%) and increased morbidity.[206] Survival benefit is limited. Informing patients of the potential high risks and poor outcomes is a critical part of the decision-making process. The role of this aggressive treatment needs further evaluation.

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Adjuvant chemotherapy

Morbidity associated with oesophagectomy often precludes patients from receiving adjuvant therapy within an appropriate time frame. Current data do not support the routine use of adjuvant chemotherapy. A meta-analysis of 1001 patients treated with adjuvant chemotherapy in six RCTs did not demonstrate improved outcomes in patients with oesophageal cancer, the majority of whom had squamous cell carcinoma.[207]

Preoperative chemotherapy

The largest study evaluating the role of preoperative chemotherapy is the UK Medical Research Council (MRC) OE02 trial. Eight-hundred and two patients were randomised to surgery alone or two 3-weekly cycles of cisplatin + 5-FU chemotherapy. The group receiving chemotherapy had significantly better OS (HR 0.79; 95% CI 0.67 to 0.93; p=0.004) and 2 year survival (43% vs 34%).[208] Updated results confirm an ongoing benefit with longer term follow-up. The benefit of preoperative chemotherapy was maintained for both DFS and OS, with corresponding HRs of 0.82 (95% CI 0.71 to 0.95; p=0.003) and 0.84 (0.72 to 0.98; p=0.03), respectively. Five-year survival with surgery alone was 17%, compared withy 23% with preoperative therapy.[209]

In contrast the US Intergroup-0113 study, which randomised 467 patients to surgery alone or three cycles of cisplatin–5-FU chemotherapy, followed by surgery and postoperative cisplatin–5-FU chemotherapy in responders, did not report a significant difference in median OS.[210] It has, however been suggested that the failure of the Intergroup-0113 study to demonstrate a survival benefit may have been due to excessive toxicity associated with the chemotherapy regimen as well as a delay to definitive surgery in patients not responding to treatment.

In a recent meta-analysis of preoperative chemotherapy, the HR for all-cause mortality for neoadjuvant chemotherapy was 0.90 (95% CI 0.81 to 1.00; p=0.05), corresponding to a 2-year absolute survival benefit of 7%. When analysed by subtype, chemotherapy did not have a significant effect on all-cause mortality for patients with squamous cell carcinoma (HR 0.88; p=0.12); however, there was a significant survival benefit in favour of preoperative chemotherapy for patients with oesophageal adenocarcinoma (HR 0.78; p=0.014).[192]

Preoperative chemotherapy is a standard of care for patients with operable mid and distal oesophageal and oesophago-gastric junctional adenocarcinoma. Ongoing studies including the MRC OEO5 trial are evaluating the optimal preoperative regimens.

There is a lack of randomised trials of preoperative chemotherapy including HRQL outcomes. One prospective study shows that preoperative chemotherapy leads to a deterioration in generic aspects of health (physical, role and social function), but a simultaneous relief in local tumour symptoms (dysphagia, eating problems and reflux).[211] Preoperative chemotherapy does not appear to delay postoperative recovery of HRQL, but persistent problems with reflux, diarrhoea and shortness of breath continue for at least 3 years after surgery.[161] A comprehensive assessment of HRQL is included in the current MRC OEO5 trial.

Gastric cancer

Perioperative chemotherapy

The MAGIC trial randomised 503 patients with adenocarcinoma of the stomach, oesophago-gastric junction or lower oesophagus to perioperative ECF (epirubicin, cisplatin and infused 5-FU), administered as three cycles before and after surgery, or to surgery alone.[212] Neoadjuvant chemotherapy resulted in tumour downstaging and did not increase the rate of postoperative complications. Perioperative chemotherapy resulted in a statistically significant improvement in OS from 23% to 36%, corresponding to an HR for death of 0.75 (95% CI 0.60 to 0.93; p=0.009). Results from the smaller French study (FNLCC ACCORD-07-FFCD 9703) utilising perioperative cisplatin and 5-FU, currently reported in abstract form only, provide additional data supporting this approach.[213]

Perioperative combination chemotherapy has therefore become the standard of care for localised gastric cancer (and type II and III oesophago-gastric junction adenocarcinoma) throughout the UK and most of Europe. Accepted perioperative regimens are ECF or ECX (epirubicin, cisplatin and capecitabine).

There is a lack of well-designed RCTs with HQRL outcomes comparing perioperative treatment strategies for tumours of the stomach or oesophago-gastric junction. The current MRC STO3 trial is addressing these issues with comprehensive assessment of HRQL.

Adjuvant chemotherapy

Several meta-analyses have been published suggesting a small survival benefit for adjuvant chemotherapy.[214–216] There is, however, considerable variation between the treatment regimens used and outcomes between Western and Asian populations. The Japanese ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) trial demonstrated a significant benefit in OS for patients receiving 12 months of S-1 (an oral fluoropyrimidine) monotherapy compared with observation after curative D2 gastrectomy (3 year OS of 80.1% vs 70.1%; p=0.0024).[217] Whether these results are applicable to a Western population remains to be seen.

Adjuvant chemotherapy alone is currently not standard practice in the UK; however, it may confer a survival benefit and should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy.

Adjuvant chemoradiotherapy

The US Intergroup 0116 trial randomised 556 patients to surgery followed by chemoradiotherapy (radiotherapy 45 Gy in 25 fractions plus bolus 5-FU/leucovorin before, during and after radiotherapy) or surgery alone. Fifty-four per cent of patients had less than D1 resections. A significant benefit in both median OS (36 vs 27 months; p=0.005) and local control rates (30 vs 19 months; p<0.001) was reported.[218] On the basis of this trial, postoperative chemoradiation became a standard of care in the USA. With longer term (>11 years) follow-up, both OS and DFS benefit has been maintained (OS, 35 vs 27 months, p=0.005; DFS, 27 vs 19 months, p<0.001).[219]

Elsewhere, however, including in the UK, there has been less enthusiasm regarding this strategy, partly due to the toxicity associated with abdominal chemoradiation but also the uncertainty as to its benefit after 'optimum' surgery. Nevertheless, it should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy, particularly those who have had suboptimal debulking.

Nutrition during chemotherapy and radiotherapy

Nutritional status may deteriorate during chemotherapy and radiotherapy as side effects of treatment such as dysphagia, sore mouth and nausea can impinge on appetite and dietary intake.

Early individualised nutrition counselling by a dietician with the use of oral supplements, if required, and weekly dietetic follow-up during and after radiotherapy has been demonstrated to contribute to a faster recover in global quality of life and

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physical function.[220] The aim of such nutrition counselling is to maintain nutritional status and minimise the side effects of the tumour and therapy. Its prolonged benefit after treatment has been demonstrated in patients with colorectal cancer receiving chemoradiation, and it is likely that this would apply to UGI tract patients.[221] If patients experience dysphagia due to tumour or treatment, then enteral nutrition should be given via an enteral feeding tube, a gastrostomy or a jejunostomy. A small study of Polyflex plastic stents suggested that these may be a good alternative to surgical jejunostomy and can be removed at the time of surgery.[222] In patients with gastric outflow obstruction, insertion of a pyloric stent can provide symptomatic relief and allow administration of chemotherapy.

Palliative treatment for oesophageal, oesophago-gastric junctional and gastric cancer

First-line palliative chemotherapy for oesophageal, oesophago-gastric junctional and gastric cancer

The benefits of palliative chemotherapy over Best Supportive Care (BSC) in the treatment of advanced gastric cancer have been demonstrated in four RCTs.[223–226] For patients considered suitable for systemic treatment, palliative chemotherapy improves median survival from 3 to 4 months with BSC alone to 7 to 10 months. Patients with advanced oesophageal cancer appear to derive the same benefits from systemic chemotherapy as those with gastric or oesophago-gastric junctional tumours, and those of good performance status should be offered combination chemotherapy.[227–229]

Several multicentre studies conducted in the UK that have defined the current standards of care in the treatment of advanced gastric or oesophago-gastric cancer have included patients with oesophageal tumours of squamous cell, adenocarcinoma and undifferentiated carcinoma histological subtypes. Many chemotherapy agents have efficacy in the treatment of advanced gastric cancer, and it is recognised that combination therapy is superior to single-agent therapy. There is, however, no international consensus regarding which combination chemotherapy regimen should be used first line.

Until recently, combination therapy with ECF has been the preferred regimen in the UK. In an RCT ECF was shown to have superior response rates (45% vs 21%, p=0.0002), median OS (8.9 vs 5.7 months, p=0.0009) and 2-year survival (13.5% vs 5.4%, p=0.03) over FAMTX (5-FU, adriamycin and methotrexate).[230 231] When compared with MCF (mitomycin C, cisplatin and infused 5-FU) in the treatment of oesophageal, oesophago-gastric junctional and gastric carcinomas, ECF had similar response rates and survival, but was preferable according to HRQL measures.[231]

Cisplatin combined with infused 5-FU (CF) is another commonly used regimen. Although ECF and CF have not been directly compared in a phase III randomised trial, a meta-analysis has demonstrated that three-drug regimens containing anthracyclines, cisplatin and 5-FU are superior to two-drug regimens containing either cisplatin/5-FU or anthracyclines/5-FU in terms of OS.[229]

The REAL-2 trial is the largest RCT evaluating first-line chemotherapy regimens for advanced oesophago-gastric cancer.[223] In a 2×2 factorial design, 1002 patients were randomised to ECF, ECX, EOF (epirubicin, oxaliplatin and infused 5-FU) or EOX (epirubicin, oxaliplatin and capecitabine). The study met its primary end points demonstrating non-inferiority in OS for capecitabine compared with infused 5-FU (HR for death, 0.86; 95% CI 0.80 to 0.99) and for oxaliplatin compared with cisplatin (HR for death, 0.92; 95% CI 0.80 to 1.10). There was no significant difference in HRQL between the four arms. EOX resulted in longer OS than ECF (HR for death 0.80; 95% CI 0.66 to 0.97; p=0.02). The combination of EOX is therefore at least as efficacious as ECF, with the additional advantages of a more convenient mode of administration (no requirement for hydration or central venous catheter insertion) and an acceptable toxicity profile. Further trials indicate that it is reasonable to substitute capecitabine for infused 5-FU, and oxaliplatin for cisplatin, in the treatment of advanced oesophago-gastric cancer.[214 232] In July 2010, the NICE appraisal of capecitabine determined that use of capecitabine in combination with platinum chemotherapy represented a cost-saving to the NHS over infused 5-FU.[227]

The V325 study is a randomised phase III trial comparing docetaxel in combination with cisplatin and infused 5-FU (DCF) with the doublet CF. A statistically significant improvement in OS (9.2 vs 8.6 months; p=0.020) was observed; however, this was at the cost of significantly more toxicity, including febrile neutropenia.[228] In a phase II Swiss trial comparing DCF with ECF, DCF resulted in a much higher rate of complicated neutropenia (41% vs 18%).[233] Docetaxel-containing regimens are not currently approved in the UK for this indication.

Patients with adequate performance status with inoperable oesophago-gastric cancer should be considered for combination chemotherapy with EOX or ECX.

First-line palliative targeted agents in combination with chemotherapy

For patients with advanced HER-2-positive oesophago-gastric junctional or gastric cancer, the addition of trastuzumab to a cisplatin and fluoropyrimidine (5-FU or capecitabine) chemotherapy doublet resulted in a statistically significant improvement in response rate (47.3% vs 34.5%; p=0.0017), progression-free survival (6.7 vs 5.5 months; p=0.0002) and median OS (13.8 vs 11.1 months; p=0.0048).[234] Tumours were considered HER-2 positive if the immunohistochemistry score was 3+ or if fluorescent in situ hybridisation (FISH) was positive for HER-2 overexpression. Trastuzumab is now licensed in the UK for patients with previously untreated metastatic HER-2-positive (defined as IHC 3+) gastric or oesophago-gastric junctional adenocarcinoma. This regimen is a valid first-line treatment option for HER-2-positive advanced gastric and oesophago-gastric junctional cancers. How this regimen compares with chemotherapy-only triplet regimens is unknown.

The use of other targeted agents, including cetuximab, panitumumab and bevacizumab, in combination with chemotherapy should remain restricted to the context of clinical trials.

Second-line palliative chemotherapy for oesophago-gastric junctional and gastric cancer

The standard treatment option for patients with advanced gastric or gastro-oesophageal junction tumours is uncertain, and wherever possible it is recommended that patients are enrolled into a RCT.

Data from phase II trials have demonstrated activity in the second-line setting for the following agents/combination regimes: irinotecan in combination with cisplatin or fluoropyrimidines, FOLFOX (folinic acid, 5-FU, oxaliplatin), docetaxel monotherapy, docetaxel in combination with oxaliplatin, and paclitaxel alone or in combination with platinum agents.[235]

Chemotherapy to downstage initially inoperable locally advanced disease for surgery

There is anecdotal evidence that in selected cases, palliative chemotherapy may result in sufficient downstaging of initially

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inoperable locally advanced disease to allow surgical resection. For instance, in the randomised trial comparing ECF with FAMTX in patients with locally advanced disease, 12 out of 43 patients treated with ECF (nine complete resections) and five out of 51 patients treated with FAMTX (four complete resections) proceeded to surgery. Of these 17 patients, nine survived for ≥2 years from randomisation.[229 231]

There have not been any randomised controlled studies to compare the addition of surgery to palliative chemotherapy with palliative chemotherapy alone. Such studies may become possible and worthwhile if minimal access surgery can be achieved with reduced complications and better recovery of HRQL than standard open surgery.

Palliative radiotherapy for oesophageal cancer

Dysphagia and pain are common symptoms associated with unresectable oesophageal cancer. External beam radiotherapy is a local palliative measure that can improve symptoms and is associated with minimal toxicity, but relief from dysphagia is often slow in onset compared with stent insertion.[236–238] Differences in outcome in terms of HRQL, dysphagia-free survival and OS between different 'locoregional' palliative treatments, particularly in the era of more effective chemotherapy, requires further investigation.

Endoscopic methods

Oesophageal intubation

Oesophageal intubation is an effective means of relieving dysphagia in a single procedure, and stents are now widely used. A Health Technology Assessment (HTA)-sponsored pragmatic RCT of the cost-effectiveness of palliative treatments for patients with inoperable oesophageal cancer studied different types of oesophageal tubes and compared these with non-stent alternatives.[239] This study confirmed the observations made previously that although the older rigid plastic tubes (Atkinson and Celestin) were cheap, they were also associated with a worse quality of swallowing and increased late morbidity. Small (18 mm) diameter self-expanding metal stents (SEMS) were as effective as large (24 mm) stents but induced less pain.

Two-thirds of patients treated with a metal stent can eat solids initially, and there appears to be little difference between the effectiveness of different types of metal stents,[240]although one small RCT suggested that covered metal stents are more effective than non-covered stents as they are complicated by less tumour ingrowth.[241] In the HTA trial, dysphagia was actually worse in 10% of patients 6 weeks after stent insertion.[239] In addition, although initial hospital stay was brief, the total number of inpatient days was in the order of 2–3 weeks, with a median survival of 4 months. There was no difference in cost or effectiveness between SEMS and non-SEMS treatments. It was concluded that an RCT of 18 mm SEMS versus non-stent treatments with survival and HRQL end points would be helpful, as would an audit of palliative patient admissions to determine the reasons and need for inpatient hospital care.

Patients can suffer acid reflux after stent insertion. A series of antireflux stents have been developed to overcome this. Several small RCTs have been performed, but results are inconclusive.[207 242] Another new development has been the introduction of plastic (Polyflex) stents. A number of small RCTs have shown that these seem to be more difficult to place and have a higher risk of late complications, particularly migration, than metal stents.[243 244] In addition, some aspects of HRQL were poorer with plastic stents.[245]

Early complications after stent insertion are unusual and, in all RCTs, procedural mortality was acceptable at ≤2%. Late complications are, however, common and occur in up to 25% of patients.[239] These include recurrent dysphagia due to tumour overgrowth for covered or ingrowth for uncovered stents, bolus obstruction and stent migration.[246] In one retrospective study, membrane degradation of covered stents occurred in 8% of cases, leading to tumour ingrowth or reopening of a tracheo-oesophageal fistula which had initially been successfully covered by a stent.[247]

The combination of radiotherapy and stents can be complicated. In patients who have had a stent placed before palliative external radiotherapy it is important to realise that stents appear to increase the radiotherapy dose delivered to the oesophageal mucosa.[248]

Patients who have been previously treated with radiotherapy who later have stents inserted are at increased risk of complications. These may include increased risk of chest pain or severe complications such as fever, bleeding, perforation and fistula formation, which rose in one study from 3% to 23%.[249–251] In another study, these findings were not confirmed.[252] Other small studies suggest that these complications are relevant only in patients with T4 disease.[253 254]

Oesophageal dilatation

As increasing numbers of patients are now treated with palliative radiotherapy, postradiotherapy strictures are increasingly common. Dilatation for these can be effective in ~80% of treatment sessions, with fewer complications than stent insertion.[255]

Brachytherapy and stents

The SIREC multicentre RCT of 12 Gy brachytherapy versus stent insertion included 209 patients in The Netherlands with inoperable oesophageal cancer. The primary outcome was relief of dysphagia during follow-up, and secondary outcomes were complications, treatment for persistent or recurrent dysphagia, HRQL and cost. Analysis was by intention to treat. Dysphagia improved more rapidly after stent placement (n=108) than after brachytherapy (n=101), but long-term relief of dysphagia was better after brachytherapy. Stent placement had more complications than brachytherapy (33% vs 21%; p=0.02), which was mainly due to an increased incidence of late haemorrhage (13% vs 5%; p=0.05). Groups did not differ for persistent or recurrent dysphagia (p=0.81), or for median survival (p=0.23). Patients undergoing brachytherapy reported significantly better role, emotional, cognitive and social function than those undergoing stent placement. Total medical costs were also much the same for stent placement and brachytherapy. The authors concluded that despite slow improvement, single-dose brachytherapy gave better long-term relief of dysphagia than metal stent placement. Since brachytherapy was also associated with fewer complications than stent placement, they recommended it as the primary treatment for palliation of dysphagia from oesophageal cancer. Unsurprisingly, physical and role function and other generic aspects of HRQL deteriorated over time before death, but the decline was more pronounced in the stent group.[256]

Given the delay to onset of benefit after brachytherapy, patient data from this study and a consecutive series (n=396) were analysed to create a prognostic model to help inform which patients should be offered stents and which should receive single-dose brachytherapy. Significant prognostic factors for survival included tumour length, WHO performance score and the presence of metastases (multivariable p<0.001) together

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with age and gender. This model could satisfactorily separate patients with a poor, intermediate and relatively good prognosis within the SIREC trial. For the poor prognosis group, the difference in dysphagia-adjusted survival was 23 days in favour of stent placement compared with brachytherapy (77 vs 54 days, p=0.16). For the other prognostic groups, brachytherapy resulted in a better dysphagia-adjusted survival.[257] The costs of both treatments were very similar.[258]

In another prospective study, the palliative effect of self-expandable stent placement was compared with that of endoluminal brachytherapy regarding the effect on HRQL and specific symptoms. Sixty-five patients with advanced cancer of the oesophagus or oesophago-gastric junction were randomised to treatment with either an Ultraflex expandable stent or high dose rate endoluminal brachytherapy with three doses of 7 Gy given in 2–4 weeks. This study was small and differences in baseline HRQL scores were observed between the two groups, but results were similar to the larger SIREC trial.[259] In a related study by the same group, stenting was considered more cost-effective than brachytherapy.[260]

Iatrogenic perforation and tracheo-oesophageal fistulae

Small retrospective case series have shown that covered metal stents can be used successfully to cover iatrogenic oesophageal perforation and tracheo-oesophageal fistulae with minimal procedural morbidity and almost zero mortality.[261 262] A small number of patients with high oesophageal tumours involving the trachea or major bronchi may benefit from tracheal stenting. This may be combined with oesophageal stenting, but tracheal stenting should always be done first to minimise the risk of causing stridor.[263]

Laser therapy and stents

Various small retrospective cost-effective analyses have compared oesophageal stenting with laser therapy. The mean survival and the cost were similar.[264 265] In a small prospective randomised trial comparing stents with laser followed by palliative radiotherapy, there was no difference in survival but the costs of laser and radiotherapy were higher than stents.[266] An RCT of 65 patients compared thermal laser ablation with stents. HRQL deteriorated in the stent group but not in the laser-treated group. Patients treated by laser lived longer than patients treated by stent insertion, but the cost of laser therapy was higher.[267]

Novel combinations of stents with other therapies

Fifty-three patients were entered into an RCT comparing treatment response with a self-expandable oesophageal stent loaded with [^{125}I]iodine seeds for intraluminal brachytherapy versus treatment response with a conventional self-expandable covered stent in patients with advanced oesophageal cancer. Dysphagia improved in both groups within the first month after stent placement, but was better in the irradiation–stent group than in the control group after 2 months ($p<0.05$). The median and mean survival times were better in the irradiation–stent group than in the control group, and the differences were significant ($p<0.001$). Haemorrhage occurred in a large number of patients in both groups in this study (30%).[268]

Photodynamic therapy

PDT using Photofrin is a relatively new technique which remains unproven. PDT was successful in relieving dysphagia for ~9 weeks in 85% of 215 patients treated in one retrospective analysis.[269] Patients living >2 months required re-intervention to maintain palliation of malignant dysphagia, and a multimodality treatment approach was common in this study. In another study, almost half the patients required a second treatment with PDT and 10% were later stented.[270] Given that skin photosensitivity after Photofrin administration lasts for 3 months, and mean survival is <6 months, this approach has a significant side effect profile. PDT has been suggested as a salvage treatment for local recurrence after chemoradiotherapy. Compared with using it as a primary therapy, the risk of complications for PDT after chemoradiotherapy is eight times higher.[271]

Argon plasma coagulation

APC has been evaluated as palliation in a few studies. A retrospective study of 31 patients described complications and tolerance. These patients underwent a median of five treatments per patient (range 1–18). Recanalisation enabling passage of the scope was achieved in 89% of treatments. The dysphagia-free interval was 25 days (range 1–175 days). Perforation was seen in three patients (10%); procedure-related mortality was 1.2%. The median hospital stay for every treatment was 2 days (range 1–27 days). APC was well tolerated, safe and effective, and is an easy and cheap technique with no further restrictions than conventional monopolar electrocoagulation.[272] A study to prospectively evaluate a new high-power system (hp-APC) evaluated palliative treatment of oesophageal cancer as one indication. The mean number of treatment sessions required was 2.3 (range 1–5). Minor complications (pain, dysphagia, neuromuscular irritation or asymptomatic gas accumulation in the intestinal wall) were observed in 13%. Major complications (perforation or stenosis) occurred in two patients (0.9%). Because of the low number of treatment sessions required, it was suggested that hp-APC could be used as an alternative to Nd:YAG laser treatment in tumour debulking.[273] APC also has value in haemorrhage and in recanalisation of blocked stents, particularly with proximal or distal luminal overgrowth.[274] This modality, nevertheless, remains experimental.

Injection therapy

In a prospective RCT comparing ethanol injection with laser therapy, both resulted in similar long-term outcomes, but patients treated with ethanol had a much higher use of analgesia, at 78% compared with 5% with laser.[275] In the HTA study, a small number had primary treatment with ethanol. All developed complete dysphagia, leading the authors to recommend that it should not be used as primary treatment.[239]

Follow-up

Regular review of patients following treatment of oesophago-gastric cancer can fulfil a number of roles including aftercare and rehabilitation following therapeutic intervention: symptom management, supportive care and surveillance. The complexity of oesophago-gastric cancer treatment frequently induces symptoms which adversely affect HQRL. Specific post-treatment side effects including dysphagia from anastomotic stricture, diarrhoea related to vagotomy and post-thoracotomy pain need appropriate management. Disorders of physiology are not uncommon and may require careful assessment and treatment by a specialist gastroenterologist. These are often insidious, and change in fat and bile salt absorption as well as bacterial overgrowth may be unrecognised by the inexperienced.

Although regular review may identify early recurrence, there is no evidence for specific investigations nor that such an approach can affect OS. Endoscopy, cross-sectional imaging and

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tumour markers have all been evaluated, but lack specificity or sensitivity. It is accepted that patients may gain psychological support from regular review, although few studies have formally evaluated this, and patients may feel more anxious prior to a planned hospital visit. Regular access to CNS support may obviate this effect. Evidence from The Netherlands shows that nurse follow-up after oesophagectomy is both cost-effective and provides equal if not better patient experience.[276]

The concept of survivorship or living beyond cancer is evolving, and experience of patient-led self-referral rather than clinic review at regular intervals is developing. This requires careful discussion and explanation of potential problems with each patient, taking into account individual risk and prognosis in the context of underlying stage of disease.

Clinical nurse specialists

The number of CNSs in the UK has increased to 1800, of which 10% are UGI CNSs.[277] However recent evidence from the NHS peer review programme show that CNS provision for UGI cancer particularly at cancer units is among the lowest for all cancer sites.[278] The role of the nurse includes clinical education, psychological support, research and consultation.[279] The extent of the CNS role is difficult to measure because of the multifaceted nature of the work, complexity of the patient pathway and the more specific requirement to respond to individual patient needs.[280 281]

Leary and colleagues have studied the work patterns of 463 CNSs (including gastrointestinal nurses) from the UK.[281] Data demonstrate that 68% of time is spent on clinical matters. of which 48% is physical care and 32% psychological care. Not surprisingly, 33% of the nurses' time is given to telephone advice and 34% spent in an outpatient setting. The remaining time is spent on administration (24%), research (2%) and education (3%).

CNSs use 'brokering' skills, provide 'clinical rescue work', advice on symptom control and support, and negotiate care pathways, all of which are intended to prevent adverse events, particularly readmission.[281 282] The impact of psychological care and tailored information given in a supportive environment improves the patients' experience and HQRL.[283] The results from the National Oesophago-Gastric Cancer Audit provide further support from patient experience surveys: 'the CNS role is the pillar in the system'.[1]

The MDT is central to patient care, with CNSs having an integral role; consulting with medical, surgical and allied healthcare professionals in order to provide a co-ordinated approach to care, enhancing quality of care and patients' well-being. Nurses also have access to important information particularly acting as the patient's advocate that may influence clinical decisions, and it is therefore essential that MDTs listen to their views.[284]

Outcomes

The assessment and evaluation of outcomes is a fundamental component of the management of oesophago-gastric cancer and was highlighted in the IOG.[149] This process is continuous and should be based around the MDT. The key to outcome measurement is high quality data documentation. Increasingly electronic systems are facilitating databases for MDT work. These do need appropriate administrative support to allow analysis and comparative audit. A recent survey of MDT functioning has stressed the need for adequate time for meetings as well as for preparation prior to meetings.[285 286]

In addition to core clinical information MDT databases should record clinical and pathological stage and details of co-morbidity and performance status and patient-reported outcomes (eg, measures of HQRL and satisfaction with care[287–289]). This will allow for case-mix in comparative audit, and information from patient-reported outcome measures can be used to follow-up patients and help with symptom control. Current initiatives within the National Cancer Intelligence Network[69] will allow timely reporting of local and national outcomes. The National Oesophago-Gastric Cancer Audit has set a high standard for evaluation of outcome and has established benchmarks which will form the basis of both qualitative and quantitative performance indicators by which services can be assessed.[1–3]

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