Gastric tumours

William R Knight
William H Allum

Abstract

Gastric tumours are subdivided into those of epithelial and stromal origin. Malignant tumours are more common than benign, with adenocarcinomas being the most common type of malignancy. Rarer gastric malignancies include gastrointestinal stromal tumours (GISTs), lymphomas and neuro-endocrine tumours. Gastric cancer is the sixth most common cancer in Europe and the fourth most common cause of cancer death. Multidisciplinary treatment planning is an essential part of management of these cancers. The only curative treatment option is surgical resection, although this is usually accompanied by perioperative chemotherapy or adjuvant chemoradiotherapy. GISTs are most commonly caused by a mutation in the *KIT* gene. They are the most common mesenchymal malignancies of the gastrointestinal tract and are usually found in the stomach. Intestinal lymphomas are also most commonly found in the stomach, and most arise from the mucosa-associated lymphoid tissue.

Keywords Gastric adenocarcinoma; gastric lymphoma; gastrointestinal stromal tumour; MRCP

Key points

- Malignant gastric tumours comprise adenocarcinoma, gastrointestinal stromal tumours, lymphomas and neuro-endocrine tumours
- Survival in adenocarcinoma remains low, at 19%, in the UK. Early detection improves survival
- The only curative treatment for gastric adenocarcinoma is surgery
- Gastric lymphoma develops in response to *Helicobacter pylori*-associated inflammation. Eradication of *H. pylori* can lead to remission
- Neuro-endocrine tumours are classified into three types based on malignant potential, with type III requiring radical surgery and chemotherapy

Introduction

Gastric tumours are classified histologically according to their tissue of origin (Table 1). Adenocarcinomas, gastrointestinal stromal tumours (GISTs), lymphomas and neuro-endocrine tumours (NETs) are the most clinically important of these and will be discussed in detail.

Gastric adenocarcinoma

Epidemiology

Gastric cancer is the sixth most common cancer in Europe, with approximately 140,000 cases diagnosed each year, and it accounts for 107,000 deaths annually. It is twice as common in male as female patients and shows marked geographical variation, with the highest prevalence in East Asia, South America and Eastern Europe. Over the last 20 years, there has been a decline in gastric non-cardiac cancers and an increase in more proximal or gastric cardiac cancers (Figure 1). The aetiology of gastric cancer varies with tumour site; *Helicobacter pylori* is commonly associated with distal disease, and obesity with cardia cancers (Table 2).[1]

Pathology

Early gastric cancer is defined as adenocarcinoma that is limited to the mucosa or submucosa, and takes no account of the size of the lesion. If an adenocarcinoma has infiltrated into or through the muscularis propria, it is defined as advanced gastric cancer. This distinction is independent of the presence of lymph node metastasis. The growth pattern of advanced gastric cancers can be polypoidal, ulcerative or locally or diffusely infiltrating (linitis plastica).

Gastric adenocarcinoma is classified histologically using the Lauren classification system into intestinal (53%), diffuse (33%) and mixed (14%) types. Intestinal type cancers are typically located in the antrum, cause hepatic metastasis and are more common in male patients. Diffuse type cancers are typically found in the body and cardia of the stomach, cause transperitoneal metastasis and are more common in young female patients.

Metastatic spread includes direct infiltration, spread via lymphatics to regional and distant lymph nodes, and haematogenous and transcoelomic spread, the latter through the body cavities. Tumour staging is based on the TNM (tumour, node, metastasis) system.

With greater understanding of the human genome, the Cancer Genome Atlas project has described four distinct genotypes of gastric adenocarcinoma:[2] (1) the Epstein–Barr virus subtype accounts for 10% of cancers and is commonly seen in fundal and body tumours in younger men; (2) the microsatellite instability subtype accounts for 20% of tumours and corresponds to the diffuse histological subtype found more commonly in older patients; (3) the genomically stable subtype comprises 20% of cancers and carries a poorer prognosis; (4) the chromosomal instability subtype, comprising 50% of cancers, correlates with the histological intestinal subtype. Understanding how these four subtypes of gastric cancer respond to treatments will guide future research and therapeutic strategies.

William R Knight *BSc MRCS is a Specialist Trainee in Surgery at the Royal Marsden NHS Foundation Trust, London, UK. Competing interests: none declared.*

William H Allum *BSc MD FRCS is a Consultant Surgeon at the Royal Marsden NHS Foundation Trust, London, UK. Research interests include perioperative treatment of oesophageal and gastric cancer. Competing interests: none declared.*

Histological classification of gastric tumours

Benign	Epithelial	Squamous papilloma
		Adenoma
	Stromal	Benign GIST
		Haemangioma
		Granular cell tumour
Malignant	Epithelial	Squamous cell carcinoma
		Adenocarcinoma
		Small cell carcinoma
		Carcinoid
		Undifferentiated carcinoma
	Stromal	Malignant GIST
	Other	Malignant melanoma
		Lymphoma
	Secondary tumours	

GIST, gastrointestinal stromal tumour.

Table 1

Diagnosis

In the UK, the National Institute for Health and Care Excellence (NICE) has introduced guidelines for symptomatic referral (Table 3), which are intended to expedite referral from primary care to endoscopy and improve early diagnosis. In particular, recent onset or persistence of dyspepsia at >55 years of age should prompt early referral for endoscopy rather than empirical treatment. In 2015, 54% of patients with newly diagnosed gastric cancers were referred from primary care, with emergency presentations accounting for 30% of cases. Endoscopy should be performed in individuals with suspected gastric cancer; it provides detailed information on tumour characteristics, including morphology and position, and allows a tissue diagnosis to be made (Figure 2).

Population-based screening in high-incidence areas such as the Far East diagnoses early gastric cancer in 60% of new cases. Fifty per cent of these have dyspeptic symptoms. However, early detection based on this experience in low-incidence areas would not be resource-efficient as dyspepsia is a non-specific symptom.

Staging

Staging of gastric cancer is described according to the 8th edition of the TNM system (see page 283 in this issue).

Once a diagnosis has been made, the initial imaging investigation should be multidetector computed tomography (MDCT) of the thorax, abdomen and pelvis. Although MDCT has an accuracy of 85% in detecting lung and liver metastases, sensitivity is low for characterizing lesions <1 cm in diameter, and for distinguishing metastatic lymph nodes from reactive lymph node hyperplasia. MDCT is also of limited value for assessing small volume ascites and peritoneal disease; these require laparoscopy and peritoneal biopsy.

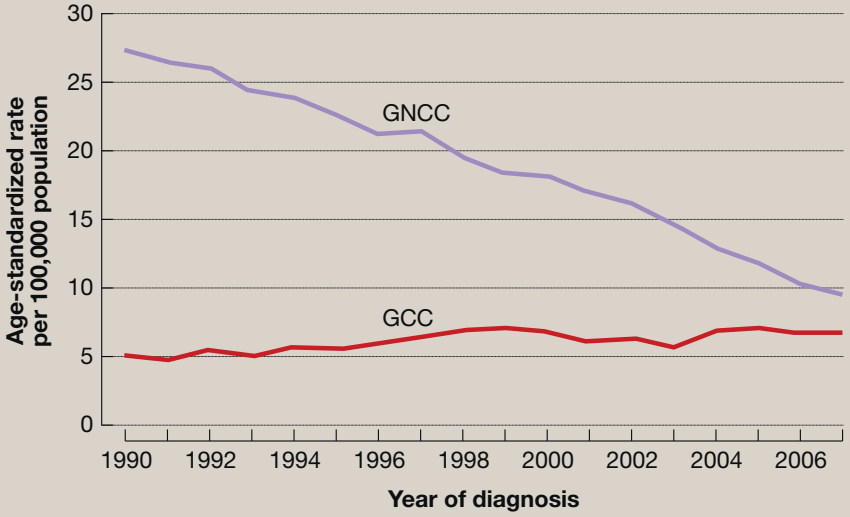
Once metastatic disease has been excluded, additional modalities can provide further detail on T and N stage. Endoscopic ultrasound can assess depth of penetration, and increases accuracy of local T staging and evaluation of local perigastric nodal involvement. It can be limited by the presence of ulceration, as inflammatory thickening can be difficult to distinguish from tumour infiltration.

Positron emission tomography combined with CT can also improve staging accuracy, detecting increased uptake of labelled glucose in malignant tissue. However, it can be limited, particularly in patients with diffuse type cancers, which demonstrate significantly less glucose uptake.

Preoperative assessment

In view of the physiological stress associated with the treatment of gastric cancer, a thorough assessment of the patient's

UK incidence rates of gastric antrum and cardia cancers



Data from the Office for National Statistics.
GCC, gastric cardiac cancer; GNCC; gastric non-cardiac cancer.

Figure 1

Aetiology of gastric adenocarcinoma

Environmental

- *Helicobacter pylori*
- Low intake of antioxidant vitamins A, C and E
- *Tsukemono* (popular salt-preserved delicacies in Japan)
- Smoking and alcohol
- Older age (peak age 70 years)
- Coal-mining, pottery
- Obesity, processed meat consumption and low fruit intake
- Exposure in early life — Japanese migrants retain a lifetime risk whereas their offspring show a risk similar to that of country of birth, suggesting a long-lasting effect from exposure to carcinogens in early life

Genetic (10%)

- Hereditary diffuse gastric carcinoma — autosomal dominant, E-cadherin gene mutation, 70% lifetime risk, risk of lobular breast cancer in 40% of female carriers, manage with either endoscopic surveillance or prophylactic gastrectomy
- Hereditary cancer syndromes — hereditary non-polyposis colorectal cancer, Li—Fraumeni syndrome, familial adenomatous polyposis coli, Peutz—Jeghers syndrome, juvenile polyposis.
- Family history
- Blood group A
- Male:female ratio 2:1

Premalignant conditions

- Pernicious anaemia
- Gastric polyps — hyperplastic, hamartomatous or inflammatory lesions <1 cm in diameter. Malignant transformation occurs in 5—10% of adenomatous or polyps >2 cm
- Gastric intraepithelial dysplasia — confined to within the lamina propria, but high-grade dysplasia is associated with adjacent carcinoma
- Gastric ulcer — treat as cancer if refractory to therapy
- Ménétrier's disease — rugal hypertrophy, hypochlorhydria and protein-losing enteropathy
- Previous gastric surgery — reflux-induced Correa stages, time interval 20 years

Table 2

NICE referral guidelines for suspected upper gastrointestinal cancer

The symptoms recommended for urgent referral (within 2 weeks) for direct access upper gastrointestinal endoscopy for suspected oesophageal or gastric cancer are:

- Dysphagia, or
- Age 55 years and over with weight loss and any of the following:
  - Upper abdominal pain
  - Reflux
  - Dyspepsia[a]

Non-urgent referral for upper gastrointestinal endoscopy is recommended for:

- Treatment-resistant dyspepsia at any age, or
- Upper abdominal pain with low haemoglobin levels, or
- Raised platelet count with any of the following:
  - Nausea
  - Vomiting
  - Weight loss
  - Reflux
  - Dyspepsia
  - Upper abdominal pain, or
- Nausea or vomiting with any of the following:
  - Weight loss
  - Reflux
  - Dyspepsia
  - Upper abdominal pain

Patients presenting with an upper abdominal mass are recommended to be referred for an urgent opinion (within 2 weeks).

[a] Dyspepsia is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting.

Table 3

preoperative fitness is vital in determining which treatment options are appropriate. A detailed clinical history should be sought, with a focus on pre-existing cardiopulmonary and renal disease. In addition to standard haematological and biochemical investigations, patients should undergo pulmonary function tests and cardiopulmonary exercise testing. Poor exercise tolerance has been shown to correlate with an increased risk of postoperative complications, independent of other patient factors. There have been encouraging early results in studies evaluating the benefit of perioperative exercise regimens.

The role of a dietitian's comprehensive nutritional assessment has been increasingly recognized in order to determine what supplementary nutrition a patient requires. Complications of treatment relate directly to poor nutritional status — a body mass index <18 kg/m^2 or weight loss >20% is associated with significantly greater rates of postoperative morbidity.

Treatment

In the UK, multidisciplinary treatment-planning is mandatory and should involve surgeons, medical and clinical oncologists, gastroenterologists, radiologists, pathologists, dietitians and specialist nurses. Although the proportion of patients suitable for radical intervention in the UK has increased in recent years, it remains low, at approximately 35% of patients, reflecting the advanced stage of disease at presentation.

Surgery: early gastric cancers can be excised endoscopically, either by endoscopic mucosal resection or (perhaps more completely) by endoscopic submucosal dissection. The meticulous and vast experience in Japan has shown that, for mucosa-only disease, the risk of lymph node metastasis is 3%, whereas for submucosal disease this rises to 20%. It is thus oncologically safe to use endoscopic techniques for mucosal early gastric cancer.

Surgical resection is the only potentially curative treatment modality, although, because of high rates of relapse, multimodal treatments are now standard. In established T2 and T3 disease, radical gastrectomy is indicated, the extent of the resection depending on the distance between the proximal tumour margin and the oesophagogastric junction. Subtotal gastrectomy can be performed if a proximal margin of 5 cm can be achieved in intestinal-type cancers, and 8 cm in diffuse-type cancers.

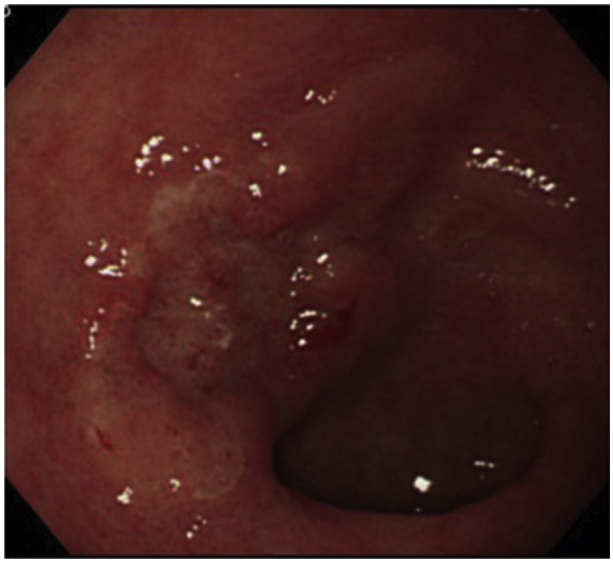


Figure 2 Endoscopic appearance of an ulcerating gastric cancer in the proximal antrum (the pylorus is seen beyond the cancer).

However, if this is unachievable total gastrectomy should be performed.

Both procedures should be accompanied by lymph node dissection. The lymphatic drainage of the stomach is divided anatomically into three tiers, with the first being perigastric nodes (N1), the second being related to the principal arterial supply to the stomach (N2), and the third being more distant (N3). Current practice is to remove the first two tiers, known as a D2 lymphadenectomy. The rationale for this is based on two large randomized trials completed in the UK (Medical Research Council (MRC)) and Holland (Dutch Gastric Cancer Group). Although early results failed to show any advantage of local node dissection over extended approaches, longer term follow-up in the Dutch trial has shown an advantage for the D2 operation. Furthermore, with increasing experience, more Western centres are reporting similar results to those in Japan, and the consensus is that, where appropriate, a D2 lymph node dissection should be performed.

Minimally invasive surgery (laparoscopic or robotically assisted) has been introduced in many UK centres as it is considered to offer potential benefits in terms of decreased operative morbidity and reduced recovery times. However, this might be at the cost of reduced nodal harvests and poorer long-term outcomes. Evidence from trials in Japan and South Korea has demonstrated results equivalent to those of open surgery in early-stage disease. Ongoing trials are evaluating whether the same outcomes can be achieved in more advanced disease, although there remain technical challenges in these procedures.

Chemotherapy and chemoradiotherapy with curative intent: gastric cancer has been confirmed by studies in advanced disease to be chemosensitive. Perioperative chemotherapy is now the standard of care that has been adopted throughout the UK and Europe. The UK MRC MAGIC trial reported an improvement in 5-year survival rate from 23% to 36% compared with surgery alone.[3] The original regimen comprised epirubicin, cisplatin and 5-fluorouracil (ECF), although many centres have replaced 5-fluorouracil with capecitabine (ECX) as it has been shown to be equally effective and avoids the need for an indwelling central venous catheter.

The North American Intergroup-0116 trial found that adjuvant chemoradiotherapy improved survival compared with surgery alone, and this has become standard practice in the USA. The CRITICS trial, however, found no difference in survival between adjuvant chemotherapy and chemoradiotherapy in patients who had been given neoadjuvant chemotherapy before surgery.[4] This trial found that only 50% of patients completed postoperative oncological treatment, emphasizing the importance of preoperative treatment in disease control. Promising early results have been seen in the FLOT4-AIO phase III trial, which is comparing perioperative FLOT (docetaxel, oxaliplatin, 5-fluorouracil) with ECX/ECF. Although the FLOT regimen is associated with increased morbidity, it has demonstrated a 50-month median survival rate, compared with 35 months for the ECX group ($p = 0.012$).[5]

Palliative treatment: palliative chemotherapy should be considered for patients with metastatic and/or locally advanced disease, and individuals with resectable disease who are not suitable for surgery (owing to co-morbidities or patient choice), as it has been shown to increase survival when compared with best supportive care. Both ECX and FLOT are being used for locally advanced disease, and a small number of patients show a response significant enough to render their disease resectable. As such, it is vital that patients are reassessed after chemotherapy as the intention of their treatment can alter. Targeted therapies are increasingly being used as understanding of the molecular biology of gastric cancer improves. Approximately 10–15% of gastric cancers are positive for human epidermal growth factor receptor 2 (HER2), and in such patients the addition of trastuzumab to chemotherapy can further prolong survival in both locally advanced and distant metastatic disease.

Complications of loco-regional disease, including outflow obstruction and bleeding, can require endoscopic stenting, surgery or radiotherapy. Patients <70 years of age with small volume metastatic disease have a better survival rate after resection.

Prognosis

The overall 5-year survival rate for gastric cancer in England has slightly improved over recent years but remains poor at 19%, contrasting with an average of 25% for Europe. Diagnosis at an early stage represents the best chance of prolonged survival.

Gastrointestinal stromal tumours

GISTs are rare tumours of mesenchymal origin and have an incidence of 1.5 per 100,000 per year. The most common site in the gastrointestinal tract is the stomach, which accounts for 60–70% of all GISTs. They can present with localized symptoms such as gastrointestinal bleeding or obstruction, although many are diagnosed incidentally in patients undergoing diagnostic endoscopy for upper gastrointestinal symptoms. Diagnosis is based on histological morphology and immunohistochemistry staining for CD117 receptors. Mutational analysis for known mutations involving the *KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) genes can confirm diagnosis, predict sensitivity to molecular targeted therapy and provide prognostic information.

Tumours <2 cm in size are considered low risk, and annual surveillance with endoscopy can be justified. Tumours ≥2 cm have greater malignant potential and should be excised. The three main factors affecting prognosis are mitotic count, tumour size and tumour rupture, the latter being the most unfavourable.

Imatinib, a tyrosine kinase inhibitor, is used as an adjuvant treatment if the risk of recurrence is high, although it should not be used in the presence of *PDGFRA* mutations as these tumours lack sensitivity to this treatment. Imatinib is the standard treatment for patients with locally advanced inoperable disease or in the presence of metastases.

Gastric lymphoma

Lymphoma can occur throughout the gastrointestinal tract, with the stomach accounting for 50–75% of cases. It commonly arises from the mucosa-associated lymphoid tissue, in response to chronic inflammation secondary to *H. pylori* infection. Eradication of *H. pylori* can lead to remission of disease. Surgery, with or without chemo-radiotherapy, is reserved for non-responsive lymphomas. The 5-year survival for localized tumours is 90–100%.

Gastric neuro-endocrine tumours

Most gastric NETs are low-grade tumours; they can be classified into three types. Type I NETs are associated with atrophic gastritis and can be removed endoscopically with good prognosis. Type II tumours show unpredictable behaviour and can metastasize. Type III tumours have a poor prognosis and require radical treatment including surgery and chemotherapy because of their greater metastatic potential. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 67-year-old man presented with a confirmed adenocarcinoma of the lesser curve of the stomach. It lay 3 cm away from the gastro-oesophageal junction. It was invading the muscularis propria but there were no distant metastases. The man was otherwise fit and well.

What is the most appropriate treatment?

A. Perioperative chemotherapy and partial gastrectomy
B. Perioperative chemotherapy and total gastrectomy
C. Total gastrectomy only
D. Endoscopic mucosal resection
E. Palliative chemotherapy

Question 2

An 75-year-old woman presented with a proximal gastric adenocarcinoma that had metastasized to the distant lymph nodes and liver. The tumour was positive for human epidermal growth factor receptor 2 (HER2).

What is the most appropriate treatment?

A. Radical total gastrectomy and synchronous liver resection
B. Palliative gastrojejunostomy
C. Chemotherapy and trastuzumab
D. Chemotherapy and radiotherapy
E. Total gastrectomy and trastuzumab

Question 3

A 55-year-old man was found to have a 4 cm gastrointestinal stromal tumour on the greater curve of his stomach. He was otherwise fit and well.

Investigations

- Haemoglobin 110 g/litre ((130–180)
- Mean cell volume 72 fl (80–96)

What is the most appropriate initial treatment?

A. Neoadjuvant imatinib
B. Surveillance
C. Surgical resection
D. Palliative imatinib
E. Radiotherapy