Tumours of the stomach

William H Allum

Abstract

Gastric tumours are either epithelial or stromal in origin. Benign tumours are rare with the majority being malignant and mostly adenocarcinomas. Gastric lymphomas, gastrointestinal stromal tumours (GISTs) and gastric carcinoid are less common and have variable cancer biology. Gastric adenocarcinoma is the eighth-commonest cancer in the UK. Proximally situated cancers are most frequent. It is characterized by late presentation with 80% of patients presenting with locally advanced or distant metastatic disease. Recognition of early gastric cancer remains a challenge in low-incidence areas. Improvements in imaging techniques have allowed more individualized, tailored and stage-related treatments. Outcome in localized cancers has improved with multi-modality therapies yet overall survival remains poor. Gastric lymphomas are the commonest gastrointestinal tract lymphoma and many arise from mucosa-associated lymphoid tissue. These are low grade but may progress to high grade lymphomas. GISTs usually have a benign biology although a third can be locally invasive and metastasize. The tumour cells express a growth factor receptor with tyrosine kinase activity, which is susceptible to targeted therapy.

Keywords Early detection programmes; junctional cancer; multi-method therapies; oesophagus and stomach; standardized surgery

Introduction

Gastric tumours are classified histologically according to their tissue of origin. The clinically important tumours are adenocarcinomas, lymphomas and gastrointestinal stromal tumours (GISTs) and these will be discussed in detail.

Gastric adenocarcinoma

Epidemiology

Worldwide there are approximately 1 million new cases of gastric cancer annually making it the fourth-commonest cancer. It is more common in the Far East and some parts of South America, with lower rates in western Europe and the USA. It is twice as common in men and the incidence increases with age, peaking in the seventh decade. Most gastric cancers arise sporadically. The associated aetiological factors are shown in Table 1.

Pathology

Pathological staging is based on the extent of local disease and distant spread. The TNM system documents stage according to features of the primary tumour (T), regional lymph nodes (N) and distant metastasis (M). Histologically it is classified into intestinal (53%), diffuse (33%) or mixed (14%) type (Lauren classification).

William H Allum *BSc MD FRCS is a Consultant Upper Gastrointestinal Surgeon at the Royal Marsden Hospital, London, UK. Conflicts of interest: none declared.*

Intestinal cancers are usually well differentiated and more often seen in distal disease, whereas diffuse cancers are poorly differentiated and seen in cardia cancers. Metastatic spread is by direct infiltration, via lymphatics to regional and distant lymph nodes, haematogenous and transcoelomic, spreading throughout body cavities. Nodal status is based on the Japanese classification of lymph node drainage, which is divided into three tiers that are related to the principal arterial supply to the stomach (N1–3, Table 2). Classification of nodal stage has been modified according to the number of nodes involved in relation to the number of nodes resected. The TNM classification has recently been revised – TNM 7. In the revision oesophageal cancer includes all cancers within 5 cm of the squamo-columnar junction. All other cancers are classified as gastric. This is a pathological classification which has been recommended for implementation by

Aetiology of gastric adenocarcinoma

Environmental

- *Helicobacter pylori*
- Low antioxidant vitamins A, C and E
- Tsukemono (popular salt-preserved delicacies in Japan)
- Smoking
- Elderly (peak age 70 years)
- Coalmining, pottery
- Obesity
- Japanese migrants retain lifetime risk and offspring show similar risk to 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 and juvenile polyposis
- Family history
- Blood group A
- Male:female (2:1)

Premalignant conditions

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

Table 1

© 2011 Elsevier Ltd. All rights reserved.

Lymph node stations according to Japanese rules

Lymph node station	
N1	
1	Right cardiac
2	Left cardiac
3	Lesser curve
4	Greater curve
5	Suprapyloric
6	Infrapyloric
N2	
7	Left gastric artery
8	Common hepatic artery
9	Coeliac axic
10	Splenic hilum
11	Splenic artery
N3	
12	Hepatoduodenal ligament
13	Retropancreatic
14	Superior mesenteric artery
15	Middle colic artery
16	Para-aortic

Table 2

the Royal College of Pathologists (see also Pathology of epithelial tumours of the stomach on pp 547—549 of this issue).

Early gastric cancer

Disease limited to the mucosa and submucosa, independent of lymph node metastasis, is defined as 'early gastric cancer'. The Japanese Endoscopic Society has described three types of early gastric cancer: protruberant (I), superficial (II) and ulcerating (III). Well-differentiated, small (<2 cm) and protruberant early gastric cancer have a virtually zero risk of nodal disease.

Site

In western countries, the most common site of oesophago-gastric cancer occurs at the gastro-oesophageal junction, reflecting the proximal migration of cancers within the stomach over the last 30 years. These are classified into three types — Siewert classification. Type I are true oesophageal cancers and are often associated with columnar cell metaplasia (Barrett's oesophagus). Type II are true carcinomas of the cardia arising from the cardiac epithelium or short segments with intestinal metaplasia at the oesophago-gastric junction. Type III are subcardial cancers that spread across the junction, but otherwise involve nodes similar to gastric cancer. This is a clinical classification and has a role in determining the appropriate operation.

Clinical features

In Japan and other areas of high incidence, endoscopic screening programmes detect early gastric cancers, often before patients become symptomatic. These established programmes have included asymptomatic populations, but such patients often have non-specific symptoms. This finding has prompted many in areas of low incidence to recommend endoscopy for those with minimal symptoms of dyspepsia before empirical symptomatic treatment has been started; such an approach increases the number of early cancers. This has been criticized because it lacks sensitivity, with large numbers of normal examinations being done for a small number of positive findings.

In the UK the National Institute for Health and Clinical Excellence has introduced guidelines for symptomatic referral (Table 3), which are intended to enhance referral from primary care for endoscopy and improve early diagnosis. Most of the included symptoms are those of established disease although recent onset or persistence of dyspepsia over the age of 55 years should initiate early referral for endoscopy rather than empirical therapy. Despite this initiative only approximately 40% of newly diagnosed gastric cancers are referred from primary care either as urgent suspected cancer or as routine and 30% present as emergencies. Many patients have experienced symptoms for at least 6 months and 75% have advanced disease at diagnosis.

Diagnosis

Endoscopy is the first-line investigation in establishing a diagnosis. It permits the tumour within the lumen to be seen and multiple biopsies taken for histological confirmation. Vital dye spraying (e.g. indigo-carmine) can accentuate early gastric cancers and facilitate targeted biopsies.

The results from a diagnostic endoscopy should include:

- description of the site of the cancer with proximal and distal limits, measured from the incisors
- relationship to specific landmarks (e.g. cardia, incisura, pylorus) and position in the stomach (lesser, greater curve)

UK National Institute for Health and Clinical Excellence guidelines for urgent referral to specialist or endoscopy

- Patient of any age with dyspepsia and any of the following:
  - Chronic bleeding of the gastrointestinal tract
  - Dysphagia
  - Weight loss
  - Vomiting
  - Iron deficiency anaemia
  - Epigastric mass
  - Suspicious barium meal
- Patient without dyspepsia:
  - Dysphagia
  - Unexplained abdominal pain and weight loss
  - Upper abdominal mass
  - Jaundice
  - Vomiting and weight loss
  - Iron deficiency anaemia
- Worsening dyspepsia:
  - Barrett's oesophagus
  - Known dysplasia, atrophic gastritis, intestinal metaplasia
  - Peptic surgery >20 years ago
- Patient aged >55 years with unexplained and persistent recent-onset dyspepsia

Table 3

© 2011 Elsevier Ltd. All rights reserved.

- description of macroscopic appearance and measurement of dimensions
- evidence of possible complications (e.g. bleeding, obstruction).

Multiple biopsies should be taken, with a minimum of four from each quadrant of an ulcerating lesion. Histology of the biopsies should confirm the tumour type and provide an indication of the degree of differentiation, acknowledging that this may not be fully representative of the whole tumour.

Staging

Once a confirmed histological diagnosis has been made staging should follow an established algorithm. A combination of multi-detector computed tomography (MDCT), laparoscopy, endoscopic ultrasound and positron emission tomography-CT (PET–CT) scanning is required.

MDCT: high-resolution dynamic two-phase CT with contrast (i.v.) and water (p.o.) to distend the stomach allows accurate assessment of distant metastatic disease. The chest, abdomen and pelvis should be scanned. MDCT has an accuracy of 85% in detecting lung and liver metastasis. Sensitivity is low for characterizing lesions smaller than 1 cm and distinguishing metastatic lymph nodes from reactive lymph node hyperplasia. MDCT is also limited for assessing small-volume ascites and peritoneal disease and these require laparoscopy and peritoneal biopsy.

Laparoscopy: is essential to assess small-volume peritoneal disease and local tumour infiltration. It can alter MDCT staging by up to 40% (upstaging or downstaging). Biopsies should be taken from suspicious lesion(s) to confirm peritoneal or visceral spread. The addition of peritoneal cytology either from free fluid or from peritoneal washings can add detection of peritoneal disease. In Japan peritoneal stage has been incorporated into the staging classification as it indicates a higher risk of peritoneal recurrence.

Endoscopic ultrasound: has become part of staging, particularly in determining the proximal limit of junctional tumours, where there is a risk of submucosal infiltration, and assessing possible tumour penetration into neighbouring structures. It is also helpful in the assessment of early gastric cancer to determine the depth of penetration. The stomach wall can be seen as five layers of alternating bright (hyperechoic) and dark (hypoechoic) bands. Penetration limited to the submucosa can be readily shown, but ulcer fibrosis into the muscle layer can be difficult to differentiate from tumour infiltration. Detection of malignant lymph nodes is limited to the perigastric nodes, and accuracy is reduced for nodes in other locations.

PET–CT: Positron emission tomography (PET) with CT image fusion can provide a functional assessment of tumour extent. PET–CT uses the principle that malignant tumours consume glucose at a faster rate than benign tissue.

It is particularly useful in detecting distant nodal disease or spread to sites outside the area covered by MDCT. There are some limitations to PET–CT as mucinous and diffuse type cancers do not take up the radiolabelled glucose analogue.

Co-morbidity assessment

Many patients with gastric cancer have significant co-morbidity partly reflecting their age but also aetiological factors such as smoking and poor dietary habits. It is as important as staging the cancer to determine the fitness of the patient in the context of their co-morbid conditions before treatment planning can occur. A careful clinical history with particular reference to cardiovascular and respiratory systems as well as hepatic and renal function is essential. In addition to standard haematological and biochemical investigations, cardiac and respiratory function tests are required. These may include echocardiography and pulmonary spirometry. Latterly there has been considerable interest in cardiopulmonary exercise testing which determines the level at which metabolism changes from aerobic to anaerobic respiration.

Complications of treatment also relate to poor nutritional status and a body mass index under 18 kg/m^2 or more than 20% weight loss should prompt the need for supplemental feeding.

Treatment

The detail from diagnostic and staging investigations as well as assessment of co-morbidity should allow an appropriate treatment plan to be developed. In the UK such a plan needs to be discussed by the multidisciplinary team to ensure all treatment options are considered for each patient irrespective of the extent of disease. Because of the late stage at presentation recent data from the UK National Oesophago-gastric Cancer Audit have shown approximately 20% of patients have disease which is suitable for radical intervention. Thus 80% of patients present with cancers which are only appropriate for palliative therapies.

Endoscopic: excision of early gastric cancer is achieved by endoscopic mucosal resection (EMR). In EMR saline is injected into the mucosa surrounding the lesion to elevate it and the lesion is removed using a polypectomy snare. This is appropriate for polypoidal or raised lesions that are small and initial biopsy shows a well-differentiated cancer. In the Far East as a result of their greater experience with EGC, excision is also undertaken by endoscopic submucosal dissection (ESD). The oncological safety of such techniques has been assured in mucosal only disease as the risk of lymph node metastasis is 3% whereas for submucosal disease this rises to 20%.

Surgical: the aim of radical surgery with curative intent is to achieve an R0 resection, which is defined as resection of all macroscopic and microscopic disease by including the primary site with a clear margin, any locally infiltrated structures and local and regional lymph nodes.

Gastric resection – the extent of gastric resection has evolved from the recommendations of the Japanese Rules for Gastric Cancer. The type of procedure is determined by the site and macroscopic size of the lesion within the stomach. A subtotal gastrectomy is recommended for an early or well-circumscribed T2 cancer if the proximal edge is more than 2 cm from the oesophago-gastric junction; a 5-cm clearance is required for a more infiltrative lesion. A total gastrectomy is recommended if the proximal distance from the junction is less than 5 cm or the tumour is diffuse with submucosal infiltration. In all cases, excision of the greater and lesser omentum is undertaken

 © 2011 Elsevier Ltd. All rights reserved.

together with the anterior leaf of the omental bursa (lesser sac). The duodenum should be divided at least 2 cm beyond the pylorus. Occasionally, if the tumour is adherent to adjacent structures such as the diaphragm, transverse colon, spleen or the body/tail of the pancreas, removal of part or whole of these organs en bloc may be necessary to obtain a macroscopically tumour-free margin. Reconstruction of gastrointestinal continuity is preferably by a Roux-en-Y jejunal loop. Most authors advocate that the loop should be placed anterior to the transverse colon to keep away from the gastric bed and minimize the potential for involvement in recurrent disease.

For junctional cancers, a proximal in situ margin of 5 cm must be achieved. A total gastrectomy is recommended for type III junctional tumours, and a transhiatal approach may be needed to achieve the clear margin and safely undertake the anastomosis. Total gastrectomy may be appropriate for type II cancers, although the proximal extent may be such that an oesophago-gastrectomy is more appropriate. Proximal-third gastric cancers have traditionally been treated by total gastrectomy. The inherent nutritional complications have stimulated interest in proximal gastrectomy with reconstruction with a jejunal or gastric tube.

There is increasing experience in minimally invasive gastric resections. Initial experience has demonstrated that the procedure is feasible and practical, and early studies have reported a reduced requirement for transfusion, a quicker return to gastrointestinal function and a shorter stay in hospital. Minimally invasive procedures have been criticized for compromising oncological principles, but experienced authors are reporting similar lymph node yields as open surgery. Further data are required in this exciting area, but developments must be led by those experienced in open procedures.

Lymphadenectomy – extended lymphadenectomy should reduce locoregional recurrence, allow more accurate staging of the disease and hence a better prediction of survival. Radicality of dissection is categorized by the level of lymph node groups excised. Lymph nodes are arranged anatomically in tiers with the first being perigastric (N1), the second being related to the principal arterial supply to the stomach (N2) and the third being more distant (N3). A D2 resection entails removal of all group N1 and N2 lymph nodes.

In the Japanese Rules, a resection:

- is 'curative' if all evidence of cancer is removed
- is 'absolute curative' if at least one tier of nodes beyond those affected is removed (e.g. D2 lymphadenectomy for N0 or N1cancer)
- is 'relative curative' if the outer tier of nodes removed has involved nodes (D = N)
- is a 'D1 or limited lymphadenectomy' if only the first tier of nodes is removed (this has been the level of resection achieved by most surgeons in western countries).

There have been numerous studies to emulate the Japanese experience in the West. Two large randomized trials have been completed in the UK and Holland and early results failed to show any advantage of local node dissection over extended approaches and there was greater operative mortality in the extended group possibly reflecting a learning curve. Latterly 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 the Japanese and the International Gastric Cancer Association consensus view (2009) is that where appropriate a D2 lymph node dissection should be performed.

Adjuvant and neoadjuvant therapies: although surgery is the principal treatment for gastric cancer, the frequent presentation of advanced disease and the limited outcome for patients after optimal surgery has driven the search for appropriate non-surgical interventions. Numerous clinical trials in advanced disease have confirmed gastric cancer is chemosensitive. Studies of the sites of relapse after curative surgery have shown that the gastric bed is the most common site of locoregional recurrence. Critics of Western surgery have claimed this reflects inadequate resection of possible sites of disease.

However there have been several large studies which have confirmed the need for additional therapy in all but the earliest stage.

Initial experience with adjuvant postoperative chemotherapy has produced a modest improvement in survival although the conclusions from all meta-analyses of adjuvant treatment have stated that this approach should only be undertaken in clinical trials. In 2007 the Japanese demonstrated a 10% benefit at 3 years with the agent S-1 (a 5 fluorouracil analogue) when used in the adjuvant setting after standard radical surgery in T3 and/or node positive disease. This study has set the standard in the Far East.

In the West there have been three studies which have established the standard of care. Two (UK MAGIC trial and the French FFCD trial) have confirmed a 13% advantage for perioperative chemotherapy with cycles given before and after surgery. This approach is now adopted by most of Europe. In the USA a trial of adjuvant chemoradiotherapy (Intergroup 116) has confirmed a durable benefit of over 10% in all patients again setting the standard.

Current and future trials are evaluating whether combinations of these approaches can add extra benefit and are also investigating whether adding targeted therapies can enhance the outcome when combined with the most effective chemotherapy combinations.

Palliative treatment: should be considered for patients with metastatic and/or extensive locoregional disease or in those with resectable disease who are not suitable for surgery, for example poor health or patient refusal. Palliative chemotherapy with a similar combination of agents as used perioperatively increases median survival from 6 to 11 months. Use of combination chemotherapy with targeted therapies (e.g. trastuzumab) has shown survival can be extended to over 13 months. Palliative surgery is very occasionally used for gastric outlet obstruction or intractable bleeding although these can be controlled with non-surgical approaches such as endoscopically placed self-expanding stents or endoscopic ablative therapy.

Prognosis

The overall 5-year survival of 12% for gastric cancer has shown little change over the last 10 years despite advances in investigation techniques and treatments. Early diagnosis offers the best

 © 2011 Elsevier Ltd. All rights reserved.

chance of prolonged survival and identification of larger numbers of patients with localized disease must be the aim of further work.

Gastric lymphoma

The stomach is the commonest site of extra-nodal presentation of non-Hodgkin lymphoma. Such tumours account for 2–5% of all gastric malignancies.

Pathology

The two main types of gastric lymphoma are MALT (mucosa associated lymphoid tissue) and DLBCL (diffuse large B cell lymphoma). MALT lymphoma arises in sites normally devoid of lymphoid tissue as a result of chronic inflammation. It is usually multifocal with a gross appearance ranging from chronic gastritis to a mass. There is a strong relationship with *Helicobacter pylori* infection which is thought to cause chronic antigenic stimulation seen on histological examination. MALT can involve extra gastric sites particularly the lung and colon.

DLBCL accounts for 40% of all gastric lymphomas. Many patients present with multifocal disease with both nodal and gastric involvement.

Diagnosis

The diagnosis of gastric lymphoma is based on endoscopic biopsy. Endoscopic ultrasound is useful in demonstrating the extent of the disease. Superficial, spreading and infiltrative patterns are usually seen in low grade MALT lymphoma whereas mass lesions are associated with high grade MALT or DCBCL. All patients should have MDCT to assess the extent of nodal and other extra-nodal disease.

Treatment

Surgery used to be the mainstay of treatment for gastric lymphoma.

However the understanding of the pathology has relegated surgery to use only in complications. A large study of patients with ulcer symptoms demonstrated MALT lymphoma to be associated with *H. pylori* in 70/151 cases contrasting with only 5/49 who did not have *H. pylori* infection. Eradication therapy of *H. pylori* resulted in eradication of both the infection and the MALT in 55% of patients. There is an appreciable relapse rate and therefore such patients should be offered lifelong endoscopic surveillance. In high-grade disease further eradication is appropriate although chemotherapy and radiotherapy are now preferred to surgery.

DCBCL is primarily treated with chemotherapy. CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone) produces up to an 86% clinical complete response. Comparisons between chemotherapy alone and chemotherapy and surgery have shown no difference when surgery is added in terms of long term survival. Indeed those presenting with complications, which formerly needed surgery, rarely need a resection.

Gastrointestinal stromal tumour (GIST)

The key to pathology reporting is the prediction of relapse. The pathological criteria take into account tumour size, mitotic index and tumour site (Table 4) (see also Pathology of epithelial tumours of the stomach on pp 547–549 of this issue).

Clinical features

Gastric GISTs comprise 39% of all GISTs. Approximately 10–30% are malignant in behaviour with metastasis to liver and peritoneal cavity.

The common presentation is with bleeding, either overt or occult, pain and fatigue or malaise. Small GISTS (<2 cm) are usually asymptomatic and are detected incidentally.

Diagnosis

An endoscopic diagnosis should be confirmed with endoscopic ultrasound (EUS). The common finding is of a submucosal mass with a mucosal ulcer on the apex. Biopsies often show normal mucosa unless deliberate deeper ones are taken. A definitive diagnosis is often not made until the lesion has been resected.

MDCT is indicated to evaluate size and local extent and metastatic disease. In patients with large lesions or liver metastases percutaneous biopsy may be required.

PET–CT scanning has been useful in assessing patients for radical surgery and is increasingly fulfilling a role in monitoring response to treatment.

Treatment

The management of small incidental (<2 cm) is controversial. If surgical removal is not performed follow-up evaluation is recommended with EUS or MDCT after 6 months and if no change a further evaluation after a further 12 months.

All asymptomatic GISTs over 2 cm should be resected. Small tumours can be resected laparoscopically.

In resectable tumours a wide local resection with macroscopic and microscopic removal of the entire tumour is recommended. Lymph node dissection is not required. En bloc resection of locally involved organs is recommended where possible. In patients with a high risk of recurrence, imatinib is recommended as adjuvant therapy.

If the tumour is not deemed resectable or if there are metastases, imatinib should be started. This may result in a response to render the tumour resectable and such patients should be entered into a trial.

Risk of relapse for gastric GIST

Size (cm)	Mitoses/50 High power fields	Risk
<2	<5	Very low (0%)
>2 <5	<5	Very low (1.9%)
<2	>5	Very low (0%)
>5 <10	<5	Low (3.6%)
>10	<5	Moderate (12%)
>2 <5	>5	Moderate (16%)
>5 <10	>5	High (55%)
>10	>5	High (86%)

Table 4

© 2011 Elsevier Ltd. All rights reserved.

Follow-up

The level of risk of recurrence determines the approach to follow-up. Very low risk can be discharged, low risk require a CT at 3 months and then clinical review, intermediate risk who are usually treated by surgery and adjuvant treatment require CT review every 6 months to 2 years and then annually to 5 years and high risk a CT at 3 months for 2 years, 6 monthly for 2 years and then annually. ◆

FURTHER READING

Griffin SM, Raimes SA, eds. Upper gastrointestinal surgery. A Companion to specialist surgical practice. 4th edn. WB Saunders Ltd, 2009.

Guidelines for the management of gastrointestinal stromal tumours (GIST) in Scotland — On line 2009.

William H Allum, Jane M Blazeby, S Michael Griffin, David Cunningham, Janusz A Jankowski, Rachel Wong. Guidelines for the management of oesophageal and gastric cancer. *Gut* — On Line, June 2011.

 © 2011 Elsevier Ltd. All rights reserved.