BMJ

BMJ 2013;347:f6367 doi: 10.1136/bmj.f6367 (Published 4 November 2013)

CLINICAL REVIEW

The diagnosis and management of gastric cancer

Sri G Thrumurthy *honorary research fellow*[1], M Asif Chaudry *oesophagogastric surgeon*[2], Daniel Hochhauser *Kathleen Ferrier professor of medical oncology*[3], Muntzer Mughal *honorary clinical professor and head*[1]

[1]Department of Upper Gastrointestinal Surgery, University College London Hospital, London NW1 2BU, UK; [2]Department of Upper Gastrointestinal Surgery, St Thomas' Hospital, London, UK; [3]UCL Cancer Institute, University College London, London, UK

Age standardised mortality rates for gastric cancer are 14.3 per 100 000 in men and 6.9 per 100 000 in women worldwide.[1] Incidence shows clear regional and sex variations—rates are highest in eastern Asia, eastern Europe, and South America and lowest in northern and southern Africa.[1] Early diagnosis is crucial because of the possibility of early metastasis to the liver, pancreas, omentum, oesophagus, bile ducts, and regional and distant lymph nodes.[2] Using evidence from large randomised controlled trials, meta-analyses, cohort studies, and case-control studies this review aims to outline preventive strategies, highlight the presenting features of gastric cancer, and guide generalists in early diagnosis, referral, and treatment.

What is gastric cancer?

Gastric cancer refers to tumours of the stomach that arise from the gastric mucosa (adenocarcinoma), connective tissue of the gastric wall (gastrointestinal stromal tumours), neuroendocrine tissue (carcinoid tumours), or lymphoid tissue (lymphomas). This review will focus on gastric adenocarcinoma (>90% of all gastric cancers), which may be polypoid, ulcerating, or diffuse infiltrative (linitis plastica) in macroscopic form.

Who gets gastric cancer?

Epidemiological data from the American Cancer Society suggest that gastric cancer is the fourth most common cancer in men (after lung, prostate, and colorectal cancer) and the fifth most common cancer in women (after breast, cervical, colorectal, and lung cancer) globally.[3] Gastric cancer accounts for 8% of the total number of cases of cancer and 10% of annual deaths from cancer worldwide. It has a significantly higher fatality to case ratio (70%) than prostate (30%) and breast (33%) cancer.[4]

Men are twice as likely as women to develop gastric cancer,[3] with an expected worldwide incidence of 640 000 cases in men and 350 000 cases in women in 2011[3] (fig 1⇓) and peak age of incidence of 60-84 years.[5 6] The global incidence of gastric cancer has decreased significantly over time—the age standardised incidence in the United Kingdom decreased from 44 per 100 000 in 1975-77 to 18 per 100 000 in 2006-08).[7] This is partly because of reductions in chronic *Helicobacter pylori* infection and smoking in the developed world and partly the result of increased use of refrigeration, availability of fresh fruit and vegetables, and decreased reliance on salted or preserved foods.[3 8]

What are the risk factors for gastric cancer?

Helicobacter pylori

H pylori infection is widely regarded as the most important modifiable risk factor for gastric cancer. More than 2 billion people are infected worldwide, although fewer than 0.5% will develop gastric adenocarcinoma.[4] A meta-analysis of 34 cohort and case-control studies found that *H pylori* carried a relative risk of gastric cancer of 3.02 (95% confidence interval 1.92 to 4.74) in high risk settings (China, Japan, and Korea) and 2.56 (1.99 to 3.29) in low risk settings (western Europe, Australia, and United States).[10]

Cigarette smoking

A meta-analysis of 42 cohort, case-cohort, and nested case-control studies across Asia, Europe, and the US found a relative risk of 1.53 (1.42 to 1.65) of developing gastric cancer in people who smoked.[11] Results from a retrospective cohort study of 699 patients, of whom 59% were current or ex-smokers, showed that tobacco use was associated with a 43% increase in disease recurrence and death from gastric cancer (hazard ratio 1.43, 1.08 to1.91; P=0.01).[12] Smoking was also an independent and significant risk factor for other measures of recurrence and survival, including five year disease-free survival (1.46; P=0.007) and overall survival (1.48; P=0.003).[12]

In a Norwegian prospective cohort study with 69 962 participants, the absolute lifetime risk of gastric cancer was 0.776% in heavy smokers (≥20 cigarettes/day), 1.511% in long term smokers (≥30 years), and 0.658% in those who had never smoked.[13]

Correspondence to: M Mughal muntzer.mughal@uclh.nhs.uk

Summary points

- The incidence of gastric cancer is highest in eastern Asia, eastern Europe, and South America, and it affects twice as many men as women
- Risk factors for gastric cancer include *Helicobacter pylori* infection, cigarette smoking, high alcohol intake, excess dietary salt, lack of refrigeration, inadequate fruit and vegetable consumption, and pernicious anaemia
- Patients present with weight loss and abdominal pain, although those with proximal or gastro-oesophageal junction tumours may present with dysphagia
- Upper gastrointestinal endoscopy with biopsy is used to confirm the diagnosis; precise tumour stage is defined by more sophisticated radiological investigations
- Multidisciplinary approach to treatment: early gastric cancer is treated with surgery alone, whereas advanced disease is usually managed with chemotherapy before and after surgery, or postoperative chemoradiation
- Metastatic disease is managed with chemotherapy or chemoradiation as well as supportive care measures

Sources and selection criteria

We searched PubMed to identify peer reviewed original articles, meta-analyses, and reviews. Search terms were gastric cancer, cancer of the stomach, gastric adenocarcinoma, gastro-oesophageal cancer, gastric neoplasm, and neoplasm of the stomach. We considered only those papers that were written in English, published within the past 10 years, and which described studies that had adequate scientific validity.

Alcohol

A meta-analysis of 44 case-control and 15 cohort studies of 34 557 cases of gastric cancer found a slightly increased risk (relative risk 1.07, 1.01 to 1.13) in people with light to moderate alcohol consumption and a greater increase (1.20, 1.01 to 1.44) for heavy alcohol drinkers (≥4 drinks/day).[14] A prospective European cohort study estimated that a high alcohol intake (>60 g/day) carried a relative risk of gastric cancer of 1.65 (1.06 to 2.58) and an absolute lifetime risk of 0.256%.[15]

Dietary salt and food preservation

A meta-analysis of cohort studies from the World Cancer Research Fund found that each gram of salt consumed each day increased the relative risk of gastric cancer by a factor of 1.08 (1.00 to 1.17).[16] A Japanese prospective cohort study with 2467 participants found an independent association between salt intake and incidence of gastric cancer. Compared with people who consumed less than 10 g of salt per day, those who consumed more than 16 g per day had a relative risk of 2.98 (1.53 to 5.82) of developing gastric cancer.[17] This correlation was stronger in the presence of *H pylori* infection and atrophic gastritis, suggesting that mucosal damage induced by salt intake increases the risk of persistent *H pylori* infection.[4]

The lack of refrigeration and use of salt based food preservatives have been associated with an increased risk of gastric cancer in socioeconomically deprived regions.[18] A cross sectional Korean study of multiple national statistics databases found a threefold decrease in age standardised mortality from gastric cancer between 1983 and 2007 (46.1/1 000 000 *v* 16.9/100 000), which was significantly and independently correlated with an increase in the number of refrigerators per household.[19]

Dietary fruit and vegetables

A Swedish cohort study of 82 002 participants and a total of 139 cases of gastric cancer found that an intake of two to five servings of fruit and vegetables a day decreased the risk of gastric cancer when compared with less than one serving a day (hazard ratio 0.56, 0.34 to 0.93). This suggested a 44% reduction in the incidence of gastric cancer with increased fruit and vegetable intake.[20] A meta-analysis of cohort studies from the World Cancer Research Fund suggested a relative risk of 0.81 (0.58 to 1.14) per 100 g per day of non-starchy vegetables and fruit consumed.[16]

Pernicious anaemia

A recent meta-analysis of 27 cohort and case-control studies found an overall relative risk for gastric cancer in pernicious anaemia of 6.8 (2.6 to 18.1).[21] Although heterogeneity between the studies was not significant at the 5% level, the quality of the studies was variable, so further high quality studies are needed to confirm this higher risk before instigating surveillance for these patients.

Genetic syndromes

Hereditary diffuse gastric cancer is a syndrome caused by a germline mutation in the *CDH1* gene, which encodes E-cadherin, a calcium dependent cell adhesion protein involved in cell-cell interaction and cell polarity. The condition is characterised by early onset (age <40 years) of diffuse gastric adenocarcinoma, an autosomal dominant inheritance pattern, and increased risk of lobular breast cancer and signet ring cell colon cancer.[22] Prospective analysis of a genetic database showed that this mutation carries a cumulative risk of gastric cancer of 67% in men and 83% in women.[23]

Lynch syndrome, an autosomal dominant syndrome involving defective DNA mismatch repair and an increased risk of colorectal and other visceral cancers, is also associated with a higher incidence of gastric cancer.[24] A Dutch prospective cohort study of 2014 people found an increased lifetime risk of gastric cancer in both men (8%) and women (5.3%),[25] prompting consideration of surveillance gastroscopy for patients with this syndrome who carry an *MLH1* or *MSH2* mutation.

How do patients with gastric cancer present?

Because patients with gastric cancer often present with vague and non-specific symptoms, the diagnosis is challenging. Data from the US National Cancer Institute suggest that patients are typically male smokers aged 60-84 years,[5] who exhibit the cardinal symptoms of upper abdominal pain and weight loss.[26] Less common symptoms are nausea, dysphagia (in proximal and gastro-oesophageal junction tumours), and evidence of melaena. Typical textbook descriptions such as Virchow's node (prominent left supraclavicular node) and Sister Mary Joseph's nodule (periumbilical nodule) are rarely seen in primary care.

A meta-analysis of 15 studies with 57 363 patients found that "alarm" features (box 1) had a pooled sensitivity of 67% (54%

to 83%), pooled specificity of 66% (55% to 79%), and a pooled positive likelihood ratio of 2.74 (1.47 to 5.24).[27] The National Cancer Institute study suggested that although these symptoms have limited predictive value, their identification will probably remain part of dyspepsia management strategies in the United Kingdom[28] and US[26] until better approaches emerge.

The table⇓ lists the common differential diagnoses of gastric cancer.

Who should be referred for further investigations?

UK consensus guidelines in 2011 recommended that patients aged 55 years or more with new onset dyspepsia and all those with alarm symptoms should undergo urgent (within two weeks) upper gastrointestinal endoscopy.[28] If macroscopic signs of tumour (ulceration, masses, or mucosal changes) are found on endoscopy, immediate referral to a specialist upper gastrointestinal surgery unit is warranted.

How is gastric cancer diagnosed?

Endoscopy and biopsy of primary tumour

British consensus guidelines recommend that the diagnosis is made by visualising a mass on endoscopy and by histological confirmation using at least six biopsy samples from the mass and adjacent tissue (fig 2⇓).[28] If the biopsy result of a suspicious lesion is negative, a repeat biopsy is needed. Pathological examination may include immunohistochemistry for HER2/neu, which is overexpressed in a subset of gastric cancers,[29] because targeted treatment may be an option for these tumours.[30]

Staging of confirmed gastric cancer

Recent advances in imaging have enabled more accurate staging, and fewer patients with advanced or incurable disease are now referred for aggressive treatment. A meta-analysis of 54 studies of 5601 patients suggested that endoscopic ultrasonography had a sensitivity and specificity of 86% and 91% for T stage tumours and 69% and 84% for N stage tumours, respectively (box 2).[31] However, owing to the limited capacity of this technique for staging mucosal disease, current UK guidelines advocate its use only for gastro-oesophageal junction tumours and selected gastric cancers.[28]

A meta-analysis of 33 patients showed that computed tomography of the abdomen detected liver metastases with a sensitivity of 74% (59% to 85%) and specificity of 99% (97% to 100%) and peritoneal metastases with a sensitivity of 33% (16% to 56%) and specificity of 99% (98% to 100%). Computed tomography of the chest is indicated only in patients with proximal or gastro-oesophageal junction tumours. Positron emission tomography combined with computed tomography has become increasingly available in tertiary centres. A recent prospective cohort study of 113 patients found that this technique detected metastatic disease with a sensitivity of 35% (19% to 55%) and specificity of 99% (93% to 100%).[32]

When imaging investigations are negative, staging laparoscopy should be used to detect peritoneal and metastatic disease under 5 mm in diameter, which may be missed even with high quality radiological imaging. Laparoscopy also enables peritoneal cytology and biopsies to be obtained from suspicious lesions and should be considered before definitive treatment. A retrospective review of 511 patients found that staging laparoscopy effectively changed treatment decisions in 28.0% of patients with gastric cancer after computed tomography and endoscopic ultrasonography.[33]

What is the approach to making a decision about treatment?

Thorough oncological staging and preoperative evaluation of fitness are vital for patients with invasive gastric cancer. Tumours that show local invasion (T4) or distant metastases (M1) are typically not amenable to curative treatment. The patient's fitness is determined by physical activity status, biological age, and comorbidities. It can be measured objectively by lung function and cardiopulmonary exercise testing. Final treatment recommendations are made at a multidisciplinary team meeting involving experienced surgeons, radiologists, pathologists, and oncologists. The final decision should be made together with the patient after the clinician carefully explains the recommended treatment.

Treatment with intent to cure—what are the options?

Surgical resection

Current UK and US guidelines recommend that all medically fit patients with regionally confined disease undergo primary surgical resection for up to stage IA tumours and surgery after neoadjuvant therapy for stage II-III tumours.[28 34] The extent of surgical resection usually depends on tumour location. Although total gastrectomy is routinely performed for proximal tumours, multicentre randomised controlled trials have shown similar survival rates after subtotal gastrectomy for distal tumours.[35 36]

The extent of lymph node dissection is a key consideration during surgery. Recent randomised controlled trials have advocated D2 lymph node dissection (perigastric nodes and nodes along the coeliac trunk) over D1 dissection (perigastric nodes only) because D2 dissection results in lower rates of locoregional recurrence and cancer related death, despite increased rates of early morbidity and mortality.[37 38] Most high volume centres currently perform modified (spleen preserving) D2 dissections.

Randomised trials of minimally invasive gastrectomy versus open surgery suggest that long term outcomes are similar, although laparoscopic procedures offer better pain control and are associated with reduced blood loss and postoperative complication rates.[39 40]

A prospective study of 827 patients found that robotic gastrectomy produced better short term and comparable oncological outcomes compared with laparoscopic gastrectomy.[41]

Early gastric cancer (T1a) can be treated with endoscopic mucosal resection if it is confined to the mucosa, less than 2 cm in diameter, of low or moderate differentiation, and exhibits no ulceration or lymphovascular involvement.[28 42]

Neoadjuvant and adjuvant treatment

Systemic treatment is given before definitive surgery (neoadjuvant) or after resection (adjuvant) to treat micrometastases and improve outcome. The pivotal Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial randomised 503 patients with cancer of the gastro-oesophageal junction or gastric body to surgery alone or three preoperative cycles of chemotherapy (epirubicin, cisplatin, 5-fluorouracil), followed when possible by three cycles after

Box 1 Alarm features suggestive of gastric cancer[26]

- New onset dyspepsia (in patients aged >55 years)
- Family history of upper gastrointestinal cancer
- Unintended weight loss
- Upper or lower gastrointestinal bleeding
- Progressive dysphagia
- Odynophagia
- Unexplained iron deficiency anaemia
- Persistent vomiting
- Palpable mass or lymphadenopathy
- Jaundice

Box 2 American Joint Committee on Cancer (AJCC) cancer staging, 2010

Primary tumour (T)

- TX: primary tumour cannot be assessed
- T0: no evidence of primary tumour
- Tis: carcinoma in situ, intra-epithelial tumour
- T1: tumour invades lamina propria, muscularis mucosae, or submucosa
- T2: tumour invades muscularis propria
- T3: tumour penetrates subserosal connective tissue
- T4: tumour invades serosa (visceral peritoneum) or adjacent structures

Regional lymph nodes (N)

- NX: regional lymph node(s) cannot be assessed
- N0: no regional lymph node metastases
- N1: metastasis in 1-2 regional lymph nodes
- N2 = metastasis in 3-6 regional lymph nodes
- N3: metastasis in ≥7 regional lymph nodes

Distant metastasis (M)

- M0: no distant metastasis
- M1: distant metastasis

Stage grouping

- Stage 0: Tis N0 M0
- Stage IA: T1 N0 M0
- Stage IB: T2 N0 M0; T1 N1 M0
- Stage IIA: T3 N0 M0; T2 N1 M0; T1 N2 M0
- Stage IIB: T4a N0 M0; T3 N1 M0; T2 N2 M0; T1 N3 M0
- Stage IIIA: T4a N1 M0; T3 N2 M0; T2 N3 M0
- Stage IIIB: T4b N0 M0; T4b N1 M0; T4a N2 M0; T3 N3 M0
- Stage IIIC: T4b N2 M0; T4b N3 M0; T4a N3 M0
- Stage IV: any T any N M1

surgery.[43] Chemotherapy resulted in a significantly greater five year survival than surgery alone (36% *v* 23%; P=0.009), indicating significant benefit for patients with stage 2 disease or higher, although the necessity for six cycles was unresolved. This has become the standard of care for resectable gastric cancer in the UK. A later multi-centre randomised trial in patients with advanced disease, which found that oxaliplatin can replace cisplatin and that oral fluoropyrimidine capecitabine can replace the inconvenient 5-fluorouracil infusion, has resulted in wider neoadjuvant use of these agents.[44]

Adjuvant chemoradiation also showed benefit in a randomised trial of 556 patients with resected adenocarcinoma of the stomach or gastro-oesophageal junction, who were randomly assigned to surgery plus postoperative chemoradiation (fluorouracil/calcium folinate for five days then 4500 cGy radiation at 180 cGy/day, five days a week for five weeks) or surgery alone.[45] One month after completing radiotherapy, two five day cycles of fluorouracil plus calcium folinate were given. The median survival of the adjuvant chemoradiation group was 36 months compared with 27 months in the surgery alone group (P=0.005). The trial was criticised for poor survival in the surgery alone arm, with only 10% of patients in the surgery arm receiving a D2 resection and D0 resection in more than 50% of patients. In addition, toxicity was high, and this regimen—although used in the US—has not been widely adopted in the UK.

A meta-analysis of adjuvant chemotherapy trials suggests that such treatment is beneficial, although the size of the effect is small and the optimal agents are unclear. Adjuvant chemotherapy was associated with a significant benefit on overall survival (hazard ratio 0.82, 0.76 to 0.90; P <0.001) and disease-free survival (0.82, 0.75 to 0.90; P<0.001), with five year overall survival increasing from 49.6% to 55.3% with chemotherapy.[46]

Patients who undergo chemotherapy for gastric cancer may develop fatigue, nausea, vomiting, alopecia, neuropathy, and other side effects specific to the agents used.[43 44] Neutropenic sepsis is potentially life threatening and may present with fever alone. Its recognition and management are crucial in the primary care setting.[47]

Where to have surgery for gastric cancer?

In recent years, cancer services have become centralised to high volume units, and studies have shown improved in-hospital outcomes when centres and surgeons are experienced at major cancer surgery.[48] Prospective nationwide data from the American College of Surgeons' national surgical quality improvement programme attributed the lower mortality rates at high volume centres to better management of postoperative complications.[49] Large prospective studies suggest that, although postoperative mortality and mid-term survival are better in high volume centres,[50] long term survival and recurrence may be independent of hospital volume.[51]

What does palliative care involve and what are the considerations?

Up to half of all patients with gastric cancer present with incurable disease and require palliative treatment.[28] Best supportive care aims to prevent or alleviate symptoms such as bleeding, obstruction, pain, nausea, and vomiting and to improve quality of life for patients and caregivers. This should be a key focus of the multidisciplinary team, taking into account performance status and patient preference, with early direct involvement of the palliative care team and clinical nurse specialists.

Treatment of advanced disease

Chemotherapy and chemoradiotherapy

Randomised trials have shown that chemotherapy improves quality of life over best supportive care alone in patients with metastatic gastric cancer.[52 53] In the UK, the epirubicin, cisplatin, and 5-fluorouracil regimen or variants including oxaliplatin and capecitabine are most widely used. In the REAL-2 study, which compared similar regimens, median survival was 9.3-11.2 months.[44]

A randomised Korean trial of patients after initial chemotherapy showed a small survival benefit from second line treatment with taxane or irinotecan based chemotherapy—5.3 months for 33 patients in the chemotherapy arm and 3.8 months in 69 patients in the best supportive care arm (hazard ratio 0.657, 0.485 to 0.891; one sided P=0.007).[52] Patient preference, performance status, and potential side effects must be factored into decisions to administer such treatment.

A fifth of patients with gastric cancer have tumours with amplification of *HER2* (erbB2).[54] The randomised ToGA (Trastuzumab with Chemotherapy in HER2-Positive Advanced Gastric Cancer) study of 594 patients showed that targeted treatment with herceptin (trastuzumab) plus chemotherapy (cisplatin with capecitabine or 5-fluorouracil) was superior to chemotherapy alone, with a median survival of 13.8 versus 11.1 months, respectively (P=0.0048).[54] For patients whose tumours showed high *HER2* expression, median overall survival was 16.0 months (15 to 19) in those assigned to trastuzumab plus chemotherapy versus 11.8 months (10 to 13) in those assigned to chemotherapy alone. The ToGA trial established this treatment as standard for *HER2* positive patients with advanced cancer.

Palliative surgery

Palliative gastrectomy may benefit patients with obstruction of the gastric outlet secondary to antral tumours, or for incomplete dysphagia caused by tumours of the cardia. The decision to manage patients palliatively should not limit the extent of surgery; a large retrospective study has shown that more radical procedures may improve survival and quality of life in eligible patients.[55] A gastrojejunostomy, which can often be performed laparoscopically, and endoscopic stenting can be performed in those who are not eligible for first line surgical procedures.

How should patients be followed up after treatment?

Routine blood tests are needed to monitor bone marrow function during chemotherapy, and nutritional monitoring is recommended after surgery (for example, vitamin B_{12} monitoring after proximal or total gastrectomy). Despite the lack of randomised evidence evaluating follow-up strategies,[28] most UK based tertiary centres review patients every four months for three years, and annually thereafter; with radiographic imaging and endoscopy performed as clinically indicated. Patients with recurrent disease may benefit from surgery if complete resection is possible, although most patients undergo salvage chemotherapy, provided they have adequate performance status.[56]

Can gastric cancer be prevented?

Primary prevention

A meta-analysis of seven randomised trials conducted in high risk regions for gastric cancer (six in Asia) showed that eradication of *H pylori* reduced the risk of gastric cancer from 1.7% to 1.1% (relative risk 0.65, 0.43 to 0.98).[57] An intention to treat analysis of a recent Chinese randomised trial of 3365 participants found that a two week course of omeprazole and amoxicillin reduced the incidence of gastric cancer by 39% within 15 years of randomisation, with similar but not significant reductions in mortality from gastric cancer.[58] The cost effectiveness of *H pylori* vaccination as long term prophylaxis against gastric cancer in the US has been extrapolated by simulation studies,[59] but evidence for the benefit of *H pylori* eradication in low risk regions is lacking.

A meta-analysis of case-control studies (14 442 cases and 73 918 controls) found that people who had ever smoked had a 43% greater risk of developing gastric cancer (odds ratio 1.43, 1.24 to 1.66) than never smokers, whereas current smokers had a 57% greater risk (1.57, 1.24 to 2.01).[60] This suggests that efforts to prevent cigarette smoking, and help people quit, would reduce the incidence of gastric cancer.

Secondary prevention

A multi-centre open label randomised controlled trial of 544 patients found that eradication of *H pylori* (with lansoprazole, amoxicillin, and clarithromycin) after endoscopic resection for early gastric cancer decreased the risk of developing metachronous gastric carcinoma (hazard ratio 0.339, 0.157 to 0.729; P=0.003) at three years' follow-up.[61] It recommended prophylactic eradication of *H pylori* after endoscopic resection of early gastric cancer to prevent the development of metachronous gastric carcinoma.

Is there a role for screening?

Screening for early gastric cancer requires the presence of an easily identifiable group with a high absolute risk. One such group might be middle aged male smokers with a history of *Helicobacter pylori* infection or other pre-malignancy, such as Barrett's oesophagus. However, absolute risk also takes into account the incidence of cancer. The large numbers of potentially high risk people and the low incidence of gastric cancer make screening programmes unfeasible in all regions but those with a high incidence of gastric cancer (such as Japan and Chile).[62] In such regions, serological screening techniques involving pepsinogens, gastrin-17 and anti-*H pylori* (or anti-Cag-A, or both) antibodies are being evaluated, in addition to photofluorography and endoscopy.[63 64] Nanomaterial based breath testing has also recently been evaluated as a screening tool—a pilot study to a large multicentre trial found that this test has a sensitivity of 89% and specificity of 90% in distinguishing gastric cancer from benign gastric disease.[65]

Is the prognosis for patients with gastric cancer improving?

A single centre Korean study of 12 026 patients with gastric cancer found that the five year overall survival rate increased from 64.0% to 73.2% (P<0.001) from 1986 to 2006.[66] A large European study of 10 cancer registries across seven countries showed similar improvements but also detected marked variation in survival rates (28.0-44.3%) between certain countries, which could not be explained by operative mortality alone.[67]

Greater access to care; better diagnostic techniques for early detection; more rational surgical strategies; lower complication rates; advances in anaesthesia, perioperative care, and nutritional care; and wider use of systemic chemotherapy have been deemed responsible for such improvements in prognosis. These factors may also partly explain the discrepancies in postoperative survival rates across the world, although quantitative data are lacking for this.[66 67]

What treatment strategies lie on the horizon?

Novel targeted biological agents are being investigated in the treatment of gastric cancer. The role of anti-angiogenic agents such as bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor) combined with chemotherapy is the subject of a randomised trial.[68] No targeted small molecules or antibodies have yet shown benefit in the management of gastric cancer, but greater understanding of the underlying molecular basis of the disease will undoubtedly suggest strategies for treatment in the future.

Contributors: SGT conceived the review, extracted evidence, and drafted the manuscript. MAC, DH, and MM coauthored the article (including article direction, interpreting the literature, and editing the manuscript). MM is guarantor.

Funding: Supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. DH was supported by CRUK grant C2259/A16569.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893-917.
2 Coupland VH, Allum W, Blazeby JM, Mendall MA, Hardwick RH, Linklater KM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. *BMC Cancer* 2012;12:11.
3 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
4 Guggenheim DE, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol* 2013;107:230-6.
5 Anderson WF, Camargo MC, Fraumeni JF Jr, Correa P, Rosenberg PS, Rabkin CS. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA* 2010;303:1723-8.
6 Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12:354-62.
7 Office for National Statistics. Cancer statistics registrations: registrations of cancer diagnosed in 2008, England. Series MB1 no 39. 2010. www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--39--2008/index.html .
8 Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, et al. Recent patterns in gastric cancer: a global overview. *Int J Cancer* 2009;125:666-73.
9 International Agency for Research on Cancer. Pathology and genetics of tumours of the digestive system. 2000. www.iarc.fr/en/publications/pdfs-online/pat-gen/bb2/bb2-cover.pdf
10 Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. *Cancer Causes Control* 2011;22:375-87.
11 Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes Control* 2008;19:689-701.
12 Smyth EC, Capanu M, Janjigian YY, Kelsen DK, Coit D, Strong VE, et al. Tobacco use is associated with increased recurrence and death from gastric cancer. *Ann Surg Oncol* 2012;19:2088-94.
13 Sjodahl K, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, et al. Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. *Int J Cancer* 2007;120:128-32.
14 Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 2012;23:28-36.
15 Duell EJ, Travier N, Lujan-Barroso L, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, et al. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Am J Clin Nutr* 2011;94:1266-75.
16 World Cancer Research Fund. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. 2007. www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf
17 Shikata K, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, et al. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer* 2006;119:196-201.
18 Kim J, Park S, Nam BH. Gastric cancer and salt preference: a population-based cohort study in Korea. *Am J Clin Nutr* 2010;91:1289-93.
19 Park B, Shin A, Park SK, Ko KP, Ma SH, Lee EH, et al. Ecological study for refrigerator use, salt, vegetable, and fruit intakes, and gastric cancer. *Cancer Causes Control* 2011;22:1497-502.
20 Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2006;15:1998-2001.
21 Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anaemia. *Aliment Pharmacol Ther* 2013;37:375-82.
22 Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 2010;47:436-44.
23 Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology* 2001;121:1348-53.
24 Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. *J Surg Oncol* 2005;90:114-33; discussion 33.
25 Capelle LG, Van Grieken NC, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. *Gastroenterology* 2010;138:487-92.
26 Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005;129:1756-80.
27 Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006;131:390-401; quiz 659-60.
28 Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449-72.
29 Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. *Ann Oncol* 2008;19:1523-9.
30 National Institute for Health and Care Excellence. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer. TA208. 2010. http://guidance.nice.org.uk/TA208.
31 Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. *Gastrointest Endosc* 2011;73:1122-34.
32 Smyth E, Schoder H, Strong VE, Capanu M, Kelsen DP, Coit DG, et al. A prospective evaluation of the utility of 2-deoxy-2-[(18) F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer* 2012;118:5481-8.
33 de Graaf GW, Ayantunde AA, Parsons SL, Duffy JP, Welch NT. The role of staging laparoscopy in oesophagogastric cancers. *Eur J Surg Oncol* 2007;33:988-92.
34 National Comprehensive Cancer Network. Gastric cancer. Version 2. 2013. www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
35 Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg* 1999;230:170-8.
36 Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989;209:162-6.

Tips for non-specialists

- The cardinal symptoms of gastric cancer include upper abdominal pain, weight loss, and dysphagia
- Any combination of the above symptoms, in the presence of risk factors, should prompt urgent endoscopy
- Refer patients with typical symptoms and a suggestive endoscopy result to a unit specialising in the treatment of gastric cancer
- Many patients with advanced gastric cancer require initial palliative therapy, which is usually provided at the referral hospital, and general palliative care thereafter

Additional educational resources

Resources for healthcare professionals

- Cancer Research UK (www.cancerresearchuk.org)—UK's leading cancer charity's website, containing information about the charity and about cancer
- National Comprehensive Cancer Network (www.nccn.org)—Not for profit alliance of leading cancer centres worldwide, featuring international expert consensus guidelines
- Uptodate (www.uptodate.com)—Evidence based clinical decision support resource written and updated by clinicians

Resources for patients

- Patient UK (www.patient.co.uk)—Comprehensive source of health and disease information for patients
- British Society of Gastroenterology (www.bsg.org.uk/patients/general/patient-information.html)—Patient information from a large gastroenterology organisation
- Cancer.net (www.cancer.net)—Oncologist approved cancer information from the American Society of Clinical Oncology

37 Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11:439-49.
38 Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453-62.
39 Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report—a phase III multicenter, prospective, randomized Trial (KLASS Trial). *Ann Surg* 2010;251:417-20.
40 Ohtani H, Tamamori Y, Noguchi K, Azuma T, Fujimoto S, Oba H, et al. A meta-analysis of randomized controlled trials that compared laparoscopy-assisted and open distal gastrectomy for early gastric cancer. *J Gastrointest Surg* 2010;14:958-64.
41 Woo Y, Hyung WJ, Pak KH, Inaba K, Obama K, Choi SH, et al. Robotic gastrectomy as an oncologically sound alternative to laparoscopic resections for the treatment of early-stage gastric cancers. *Arch Surg* 2011;146:1086-92.
42 Bennett C, Wang Y, Pan T. Endoscopic mucosal resection for early gastric cancer. *Cochrane Database Syst Rev* 2009;4:CD004276.
43 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
44 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46.
45 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.
46 Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010;303:1729-37.
47 National Institute for Health and Care Excellence. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. CG151. 2012. http://publications.nice.org.uk/neutropenic-sepsis-prevention-and-management-of-neutropenic-sepsis-in-cancer-patients-cg151.
48 Coupland VH, Lagergren J, Luchtenborg M, Jack RH, Allum W, Holmberg L, et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008. *Gut* 2013;62:961-6.
49 Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009;361:1368-75.
50 Dikken JL, Dassen AE, Lemmens VE, Putter H, Krijnen P, van der Geest L, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. *Eur J Cancer* 2012;48:1004-13.
51 Enzinger PC, Benedetti JK, Meyerhardt JA, McCoy S, Hundahl SA, Macdonald JS, et al. Impact of hospital volume on recurrence and survival after surgery for gastric cancer. *Ann Surg* 2007;245:426-34.
52 Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev* 2010;3:CD004064.
53 Kang JH, Lee SI, Lim do H, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30:1513-8.
54 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97.
55 Zhang JZ, Lu HS, Huang CM, Wu XY, Wang C, Guan GX, et al. Outcome of palliative total gastrectomy for stage IV proximal gastric cancer. *Am J Surg* 2011;202:91-6.
56 Song KY, Park SM, Kim SN, Park CH. The role of surgery in the treatment of recurrent gastric cancer. *Am J Surg* 2008;196:19-22.
57 Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151:121-8.
58 Ma JL, Zhang L, Brown LM, Li JY, Shen L, Pan KF, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst* 2012;104:488-92.
59 Rupnow MF, Chang AH, Shachter RD, Owens DK, Parsonnet J. Cost-effectiveness of a potential prophylactic Helicobacter pylori vaccine in the United States. *J Infect Dis* 2009;200:1311-7.
60 La Torre G, Chiaradia G, Gianfagna F, De Lauretis A, Boccia S, Mannocci A, et al. Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. *Tumori* 2009;95:13-22.
61 Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392-7.
62 Lagergren J, Ye W, Bergstrom R, Nyren O. Utility of endoscopic screening for upper gastrointestinal adenocarcinoma. *JAMA* 2000;284:961-2.
63 Rugge M. Secondary prevention of gastric cancer. *Gut* 2007;56:1646-7.
64 Kato M, Asaka M. Recent development of gastric cancer prevention. *Jpn J Clin Oncol* 2012;42:987-94.
65 Xu ZQ, Broza YY, Ionsecu R, Tisch U, Ding L, Liu H, et al. A nanomaterial-based breath test for distinguishing gastric cancer from benign gastric conditions. *Br J Cancer* 2013;108:941-50.
66 Ahn HS, Lee HJ, Yoo MW, Jeong SH, Park DJ, Kim HH, et al. Changes in clinicopathological features and survival after gastrectomy for gastric cancer over a 20-year period. *Br J Surg* 2011;98:255-60.
67 Lepage C, Sant M, Verdecchia A, Forman D, Esteve J, Faivre J. Operative mortality after gastric cancer resection and long-term survival differences across Europe. *Br J Surg* 2010;97:235-9.
68 Van Cutsem E, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol* 2012;30:2119-27.

Accepted: 18 October 2013

Cite this as: *BMJ* 2013;347:f6367

Table

Table 1| Common conditions that can mimic the symptoms of gastric cancer

Differential diagnosis	Features suggestive of cancer	Differentiating investigations
Benign oesophageal stricture	No history of gastro-oesophageal reflux disease	Endoscopy and biopsy
Peptic ulcer disease	Overt gastrointestinal bleeding, weight loss, early satiety, palpable masses or lymphadenopathy, jaundice, progressive dysphagia, recurrent vomiting	Endoscopy and biopsy; patients with peptic ulcers should undergo repeat endoscopy after treatment to assess healing
	Family history of cancer	
	Age of symptom onset >55 years	
Achalasia*	Duration of symptoms <6 months	Oesophageal manometry, endoscopy, and biopsy*
	Age at presentation >60 years	
	Substantial weight loss relative to symptom duration	

*Gastro-oesophageal cancer that initially presents with the clinical and investigative findings of achalasia is known as pseudoachalasia.

Figures

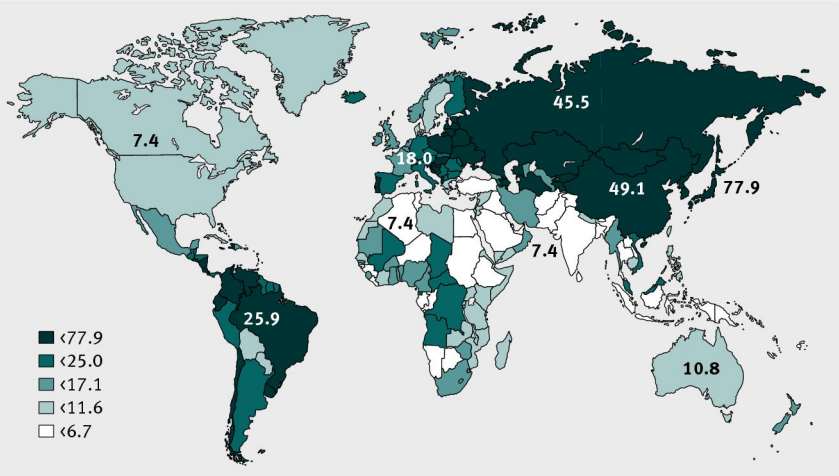

Fig 1 Worldwide annual incidence (per 100 000) of gastric cancer in men. Numbers on the map indicate regional average values. Adapted, with permission, from an article by the International Agency for Research on Cancer[9]

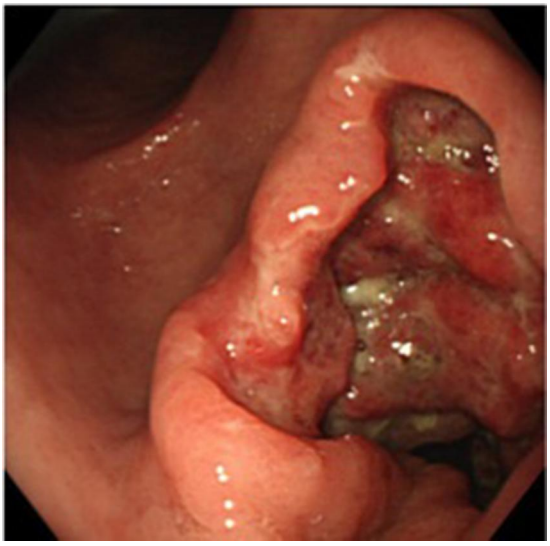

Fig 2 Endoscopic image of an advanced ulcerated gastric tumour