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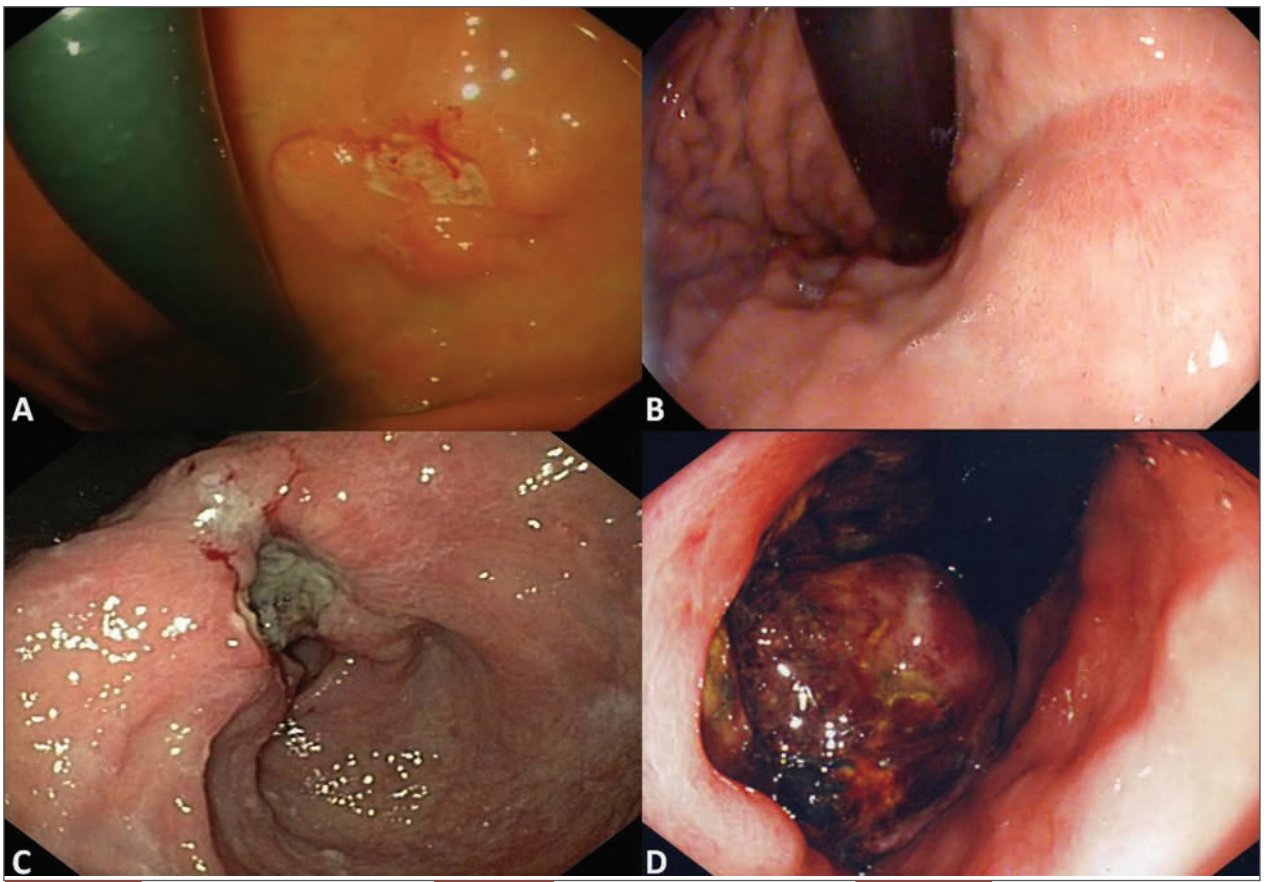


FIGURE 1
Gastric cancer at endoscopy. Early T1 lesions are difficult to see and careful inspection at endoscopy is required with some lesions visible only when the endoscope tip is retroflexed back on itself to view blind spots that would be missed on a forward viewing only examination (A). If, as in this case, very early lesions are found they can potentially be removed at endoscopy (B). However, gastric cancers are usually advanced at presentation with alarm symptoms (C) and most are incurable (D)

What are the risk factors for gastric cancer?

THE INCIDENCE OF GASTRIC CANCER HAS HALVED IN THE PAST 20 YEARS BUT IT IS STILL the seventh and eighth most common cancer in men and women respectively.[1] The decline in gastric cancer in the UK has been mirrored worldwide and is thought to be associated with a reduction in *Helicobacter pylori* infection and changes in diet in developed countries.[2] However, despite this decline, gastric cancer often presents late and the mortality ratio remains one of the highest (0.7) compared with more common cancers such as colorectal cancer (0.39), prostate cancer (0.25) and breast cancer (0.22).[1] Early diagnosis improves survival in this potentially curable cancer. Recognition of symptoms and risk factors should prompt early referral for endoscopy.

Gastric cancer in this article refers to gastric adenocarcinoma which arises from the mucosal lining and accounts for 95% of cancers related to the stomach.

There are also some rare, and sometimes more benign, forms of gastric cancer that arise in the muscle layer of the gastric wall (stromal tumours), neuroendocrine cells (carcinoid tumours), or lymphoid tissue (lymphomas).

How should diagnosis be confirmed?

What are the management approaches?

RISK FACTORS

Demographics

Men are twice as likely as women to develop gastric cancer; in 2012 the incidence was 17.8/100,000 in men and 7.2/100,000 in women. The vast majority of cases (96%) occur in people above the age of 55.[1] There are significant worldwide variations with a high incidence in selected areas of Central and South America and East Asia (> 25/100,000) but gastric cancer is relatively rare in North America and North Western Europe.[3] »

Table 1

Upper gastrointestinal cancer alarm symptoms that should prompt referral and investigation[26-28]

Alarm symptoms
- Chronic gastrointestinal bleeding
- Dysphagia
- Progressive unintentional weight loss
- Persistent vomiting
- Iron deficiency anaemia
- Epigastric mass
- Suspicious barium meal result
- Unexplained upper abdominal pain and weight loss, with or without back pain
- Obstructive jaundice

In patients with unexplained worsening of their dyspepsia and known cancer risk factors:
- Barrett's oesophagus
- Atrophic gastritis or intestinal metaplasia
- Peptic ulcer surgery more than 20 years ago

Helicobacter pylori

H. pylori prevalence in gastric cancer is estimated to be 90%.[4] Given that the prevalence of infection is very high worldwide it has been estimated that *H. pylori* accounts for > 50% of all new cases of gastric cancer[5] and its presence carries a relative risk of 2.56 for gastric cancer in western Europe.[6] *H. pylori* eradication trials in high-risk areas have shown a subsequent reduced risk of gastric cancer over 4-10 years from 1.7% to 1.1%.[7] This has led to recommended population screening and antibiotic treatment of *H. pylori* in high-risk countries.[8]

As yet there has been no benefit shown for *H. pylori* eradication in lower risk areas such as North America and the UK. The National Screening Committee found that overall, the potential psychological harm outweighed the potential benefits of a national *H. pylori* and stomach cancer screening programme in the UK where the incidence of stomach cancer is low.[9] A further analysis showed a possible cost benefit from *H. pylori* screening but concluded that before screening can be recommended further evidence is required on the effectiveness of *H. pylori* eradication on reducing risk of gastric cancer in low-risk populations.[10]

Smoking

Smoking is associated with a 60% increased risk of stomach cancer. The risk ratio in current smokers is 1.6 and in previous smokers 1.2.[11] It has been estimated that smoking is responsible for more than 10-15% of all cases but if smokers quit the additional risk recedes after ten years.[11,12] The recent decline in smoking prevalence in men from developed countries may account in part for the fall in gastric cancer rates.[13]

Alcohol and diet

A heavy alcohol intake (50-60 g/day or 6-7 units/day) has been shown to have an increased risk of gastric cancer, OR 1.2-1.65, with no excess risk demonstrated with moderate or mild alcohol intake.[14,15]

A high salt intake has a definite role. It has been shown that compared with people who consumed less than 10 g of salt per day, those who consumed more than 16 g per day have a relative risk of 2.98 of developing gastric cancer.[16] There is evidence in mice that a high-salt diet increases the chance of *H. pylori* colonisation and also may potentiate gastric cancer risk by causing changes such as glandular atrophy and crypt hyperplasia in the gastric mucosa.[17]

An increased fruit and vegetable intake can result in a 44% reduction in the incidence of gastric cancer.[18] Increased use of refrigeration, availability of fresh fruit and vegetables, and a reduction in the reliance on salted or preserved foods is a further explanation for the decrease in gastric cancer incidence.[19]

'Smoking is associated with a 60% increased risk of stomach cancer'

Pernicious anaemia

The overall relative risk for gastric cancer in pernicious anaemia is 6.8.[20] However, despite this high risk surveillance evidence is lacking. The American Society for Gastrointestinal Endoscopy recommends a single endoscopic evaluation, but does not recommend routine follow-up surveillance thereafter.[21] In comparison, the European guideline recommends follow-up every three years for patients with extensive gastric atrophy.[22] National UK guidelines recommend endoscopy if dyspepsia develops even without alarm symptoms, see table 1, above. Therefore given the lack of agreement in pernicious anaemia guidelines, all patients with pernicious anaemia should be offered a gastroscopy and gastric biopsy to check for gastric atrophy severity if not done at diagnosis. A single gastroenterology review can then be performed and a decision made with the patient regarding future surveillance benefits.

Genetic syndromes

Hereditary diffuse gastric cancer is a rare autosomal dominant condition usually presenting under the age of 40. The condition is associated with a CDH1 gene mutation and carries a cumulative risk of gastric cancer of 67% in men and 83% in women. Affected individuals should be offered total gastrectomy as screening is not thought to be effective.[23]

In hereditary non-polyposis colorectal cancer gastroscopy surveillance is recommended every two years from the age of 50 to 75 because of the increased risk of gastric cancer (standardised incidence ratio 3.4).[24] However, there is no evidence that this approach reduces mortality.[25]

PRESENTATION

Alarm symptoms

Specific at-risk or alarm symptoms for oesophago-gastric cancer have been highlighted in guidelines by NICE,[26] SIGN,[27] and the British Surgical and Gastroenterological Societies.[28] These guidelines specify the symptoms that should prompt urgent referral and investigation, see table 1, above left.

The presence of alarm symptoms and dyspepsia has a low positive predictive value (4%) but a high negative predictive value (98%) with respect to gastric cancer.[29] A study based on alarm symptoms for rapid access endoscopy showed dysphagia, weight loss and age over 55 years were significant predictors of cancer (finding 92% of cancer patients), but uncomplicated dyspepsia in patients over 55 years was not helpful.[30] Therefore it is accepted that alarm symptoms have a low predictive value, but it is recommended that they should be used in dyspepsia management for predicting gastric cancer until better approaches emerge.[28]

It has recently been demonstrated that the use of alarm symptoms alone to select patients for endoscopy results in patients with localised disease being overlooked.[31] Hence, patients with at-risk conditions who

Table 2

Tumour, Nodal, Metastases classification of gastric cancer [44]

Primary tumour (T)	
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour penetrates subserosal connective tissue without invasion of peritoneum
T4a	Tumour invades serosa (visceral peritoneum)
T4b	Tumour invades adjacent structures
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

develop dyspepsia should also be considered for urgent endoscopy.

In summary, all patients presenting with dyspepsia and either alarm features or known conditions that increase the risk of gastric cancer should be referred for urgent endoscopy, see table 1, p24.

Uncomplicated dyspepsia

There is an absence of alarm symptoms at the initial presentation in up to 50% of patients with gastric cancer,[32] and in those with alarm symptoms the vast majority have advanced disease.[33] Diagnosis at an early stage greatly improves outcomes and 70% of patients with early gastric cancer have symptoms of uncomplicated dyspepsia.[34] Therefore given that the majority of gastric cancer cases occur in people over 55, urgent endoscopy is also recommended in this group with new uncomplicated dyspepsia prior to treatment, even without alarm symptoms or if the symptoms respond to treatment, see table 1, p24.[26-28]

In patients under 55 gastric cancer presenting with uncomplicated dyspepsia is extremely rare and the majority of young patients have alarm symptoms by the time of presentation.[35,36]

Many studies[37-39] have shown that *H. pylori* testing and treatment is as effective as endoscopy in the initial management of patients under 55 presenting with uncomplicated dyspepsia. This strategy is supported by many guidelines as the number of missed cancers in patients with uncomplicated dyspepsia is extremely low. However, this approach relies on attentive primary care follow-up after *H. pylori* eradication therapy to ensure lack of response or unexplained persistent symptoms are followed up to prevent delays in diagnosis.

CONFIRMING DIAGNOSIS

Endoscopy

Upper GI endoscopy with biopsy is the recommended investigation to confirm gastric cancer. Gastric cancer can sometimes appear very similar to a gastric ulcer therefore a biopsy and histological differentiation is required. If biopsies are benign follow-up gastroscopy performed after six weeks of anti-acid treatment is performed to ensure healing or to obtain repeat biopsies.

Despite improved advances in endoscopic imaging failure to diagnose gastric cancer at the patient's first endoscopy is consistently around 10% hence patients require a second gastroscopy.[40, 41] The principal factors associated with the need to re-endoscope are failure to suspect malignancy and (as a consequence) failure to take adequate numbers of biopsies.

Gastroscopy should be carried out when the patient has been off proton pump inhibitor (PPI) therapy for two weeks if possible as PPIs may mask endoscopic findings or alter the appearance of malignant ulcers.[41, 42] Barium studies have a poor sensitivity for the diagnosis of malignancy and therefore are not the investigation of choice, histological sampling is also unavailable to differentiate between malignant and benign ulceration.

Gastric cancer staging

If a gastric lesion highly suspicious of gastric cancer is seen at gastroscopy, the patient is warned and referral to a specialist upper GI surgery unit is made. Thorough staging and high quality imaging has reduced the number of patients with advanced or incurable disease undergoing significant surgery. Gastric cancer staging employs the Tumour, Nodal, Metastases (TNM) classification system, [44] see table 2, above.

Computed tomography (CT) of the abdomen and pelvis is performed to detect local invasion. It has a sensitivity of 74% for liver metastases. It is also able to detect peritoneal metastases but with a lower sensitivity of 33%,[45] hence when CT imaging shows potentially operable disease a staging laparoscopy is indicated. This can detect peritoneal and metastatic disease under 5 mm in diameter, and enables peritoneal cytology and biopsies to be obtained from suspicious lesions.

Staging laparoscopy can change treatment decisions to perform invasive surgery in up to 28% of patients with gastric cancer after CT.[46]

Positron emission tomography (PET) combined with CT has become increasingly available in tertiary centres as an alternative sensitive method of metastasis assessment and is currently used in oesophageal cancer staging and in gastric cancers that cross the gastro-oesophageal junction into the oesophagus, but not as standard in gastric cancer staging.

The stage of the cancer is closely related to prognosis emphasising the need to diagnose gastric cancer at an early stage, see table 3, p26.[44]

'PPIs should be stopped 2 weeks before diagnostic endoscopy if possible to improve detection of gastric cancer'

MANAGEMENT

Management options are discussed at a specialist upper gastrointestinal multidisciplinary team meeting involving experienced surgeons, radiologists, pathologists, oncologists and cancer nurse specialists. The results of investigations are coupled with the patient's fitness for surgery and/or chemotherapy and the final decision made with the patient after careful explanation and discussion about the recommended treatment options. Tumours that show local invasion (T4) or distant metastases (M1) are not amenable to curative treatment.

Curative treatment

Patients deemed medically fit should undergo surgical resection to cure early gastric cancer (stage I) and chemotherapy (neoadjuvant) followed»

Table 3

Staging of gastric cancer using the Tumour, Nodal, Metastases classification and associated five-year survival[44]

Stage	Five-year survival	Tumour (T) Nodal (N) Metastases (M) stages
IA	71%	T1, N0, M0
IB	57%	T2, N0, M0; T1, N1, M0
IIA	45%	T3, N0, M0; T2, N1, M0; T1, N2, M0
IIB	33%	T4a, N0, M0; T3, N1, M0; T2, N2, M0; T1, N3, M0
IIIA	20%	T4a, N1, M0; T3, N2, M0; T2, N3, M0
IIIB	14%	T4b, N0, M0; T4b, N1, M0; T4a, N2, M0; T3, N3, M0
IIIC	9%	T4b, N2, M0; T4b, N3, M0; T4a, N3, M0
IV	4%	Any T, Any N, M1

by surgical resection for higher stage tumours (stage II-III).[28]

A total gastrectomy is performed for proximal gastric tumours, and a subtotal gastrectomy for distal tumours.[47] Multiple lymph nodes are also removed including coeliac nodes if possible as despite increased risk of early morbidity this is outweighed by the overall benefit of lowering the risk of recurrence and cancer-related death.[48] Laparoscopic procedures are possible and offer better post-operative pain control and can be associated with lower complication rates and comparable outcomes[49] with current in-hospital mortality following surgery for cancer in the UK audit reported at 1.3-3.6%.[50]

Peri-operative combination chemotherapy has now become the standard of care for localised gastric cancer throughout the UK and most of Europe. For stage II or higher gastric cancers three preoperative cycles of neoaduvant chemotherapy (epirubicin, cisplatin, and infused 5-fluorouracil), followed when possible by three cycles after surgery are recommended.[51] This results in a significantly greater five-year survival than surgery alone (36% versus 23%).

Very early gastric cancer (T1a) can be treated with endoscopy (mucosal resection) if it is confined to the mucosa and less than 2 cm in diameter. However, despite promising results from East Asia these lesions are rarely found at this stage in the UK, see figure 1A, p23,[28] with more than 50% of patients at presentation having advanced incurable disease, see figure 1D, p23.

Palliative treatment

Palliative chemotherapy can be offered for the treatment of advanced gastric cancer, with a median increased survival improved from 3-4 months to 7-10 months.[52]

For patients with advanced HER-2-positive gastric cancer (tested on the biopsy sample), addition of trastuzumab can result in a significant improvement in response rate and median overall survival (13.8 vs 11.1 months).[53, 54]

In distal gastric cancers causing upper GI obstruction, surgical jejunostomy can be performed or insertion of a pyloric stent can provide symptomatic relief. The standard treatment option for patients with advanced gastric tumours is uncertain, and where possible patients should be enrolled in a randomised trial.[28]

Patient support and follow-up

Review by a dietician and input from a cancer nurse specialist have been demonstrated to contribute to a faster recovery and better quality of life.[55] The cancer nurse has a central role, consulting with multiple specialties and primary care to provide a co-ordinated approach and acting as the patient's advocate.[56]

Regular review of patients following treatment of gastric cancer is required to manage post-treatment side effects such as dysphagia and diarrhoea following surgery and post-operative pain. Regular access to specialist nurses has been shown to be cost effective in supporting follow-up.[57]

FUTURE DIRECTIONS

The assessment and evaluation of outcomes is a fundamental component of the management of gastric cancer and the National Oesophago-Gastric Cancer Audit has set a high standard.[50] With drivers like this it is encouraging to see cancer registries across Europe showing slight improvements in five-year survival rates from 23.3% in 1999-2001 to 25.1% in 2005-2007. However they are generally still poor and vary across Europe (32.4% in Italy to 16.0% in Denmark) with the UK having one of the lowest five-year survival rates at 17.2%.[58,59]

Therefore prevention may be the key. Despite not recommending *H. pylori* screening in the UK the national screening committee did suggest a pilot of *H. pylori* screening in all 40-49 year olds and then all individuals as they reached the age of 40. This would define the effect of *H. pylori* eradication on cancer incidence in low-risk populations,[9] and possibly make way for a screening programme in selected individuals.

In the meantime gastric cancer continues to pose a diagnostic challenge which requires a vigilant low threshold for early referral and meticulous early endoscopy to make successful treatment possible.

Further reading

Guidelines for the management of oesophageal and gastric cancer
www.bsg.org.uk/clinical-guidelines/gastroduodenal/guidelines-for-the-management-of-oesophageal-and-gastric-cancer.html

SIGN87. Management of oesophageal and gastric cancer
www.sign.ac.uk/pdf/sign87.pdf

NICE CG27. Referral guidelines for suspected cancer
www.nice.org.uk/guidance/cg027

National Oesophago-Gastric Cancer Audit 2013
www.hscic.gov.uk/catalogue/PUB11093/clin-audi-supp-prog-oeso-gast-2013-rep.pdf

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key points

SELECTED BY

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Gastric cancer often presents late and the mortality ratio remains one of the highest compared with more common cancers. Early diagnosis improves survival in this potentially curable cancer. Men are twice as likely as women to develop gastric cancer. The vast majority (96%) of cases occur in people above the age of 55.

Dysphagia, weight loss and age over 55 are significant predictors of cancer. All patients presenting with dyspepsia and either alarm features or known conditions that increase the risk of gastric cancer should be referred for urgent endoscopy. Given that the majority of gastric cancer cases occur in people over 55, urgent endoscopy is also recommended in this group with new uncomplicated dyspepsia prior to treatment, even without alarm symptoms or if the symptoms respond to treatment.

***H. pylori* prevalence in gastric cancer is estimated to be** 90% and *H. pylori* accounts for > 50% of all new cases of gastric cancer. Irrespective of age, patients should be reviewed after *H. pylori* eradication treatment. For those with recurrent or persistent symptoms the need for further assessment, including endoscopy, should be considered.

Upper GI endoscopy with biopsy is the recommended investigation to confirm gastric cancer. Gastroscopy should be carried out when the patient has been off proton pump inhibitor (PPI) therapy for two weeks if possible as PPIs may mask endoscopic findings or alter the appearance of malignant ulcers.

Patients deemed medically fit should undergo surgical resection to cure early gastric cancer and chemotherapy followed by surgical resection for higher stage tumours. Tumours that show local invasion or distant metastases are not amenable to curative treatment. More than half of all patients with gastric cancer present with incurable disease and palliative chemotherapy has a small but significant effect on survival.

Useful information

Cancer Research UK
www.cancerresearchuk.org/cancer-help/type/stomach-cancer/

Macmillan Cancer Support
www.macmillan.org.uk/Home.aspx

The Practitioner online

Special Interest: Cancer
All articles on cancer in the journal online now appear with direct links to the current evidence base including:

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- Results of pre-defined search requests made to NHS Evidence, the database provided by NICE

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