Gastric cancer

Gastric cancer is the fifth most common cancer in the world and the third leading cause of cancer death in both sexes worldwide (783,000 deaths,1 in every 12 deaths globally). Rates are twice as high in men than in women. Among men, it is the most commonly diagnosed cancer and the leading cause of cancer death in several Western Asian countries, including Iran, Turkmenistan and Kyrgyzstan. Incidence rates are highest in South Korea. Mongolia and Japan also have high rates whereas the rates in Northern America and Northern Europe are generally low and are equivalent to those seen across the African regions.[1] It is a difficult disease to cure in Western countries, mainly because most patients present with advanced disease. The endoscopic screening programme in Japan has led to early detection of preventable disease.

Epidemiology[2] [3]

- The most recent statistics quoted on the Cancer Research UK website are for 2017. This shows that 6,300 new diagnoses of gastric cancer were made in the UK in 2017.
- There are unexplained wide international variations, being especially common in South Korea, Japan, China and parts of South America.
- In recent years there has been an anatomical shift from distal to proximal stomach cancer in the USA which parallels the increasing incidence of distal oesophageal carcinoma. The proximal lesser curvature, cardiac and oesophagogastric junction are the most common sites in Western countries, whereas non-proximal continues to predominate in Japan.[4]

Risk factors[2] [4]

- Increasing age: around half (51%) of all new stomach cancer cases in the UK are diagnosed in people aged 75 and over.
- It is more common in men than in women. In the UK, the ratio is 1.8:1.

- It is strongly associated with poor socio-economic status.
- *Helicobacter pylori*: this can double the risk of gastric cancer in infected individuals. A certain type of *H. pylori* (cagA-positive) can increase the risk even more. The relationship between infection and cancer in the cardia region, however, is currently unclear and it is possible that eradication of *H. pylori* may increase the risk of cardia cancer.[5]
- Diet: diets where levels of fresh fruit and vegetable consumption are low increase the risk of gastric cancer. A high level of salt and preserved foods may also increase the risk.
- Smoking.
- Atrophic gastritis, pernicious anaemia, post-gastrectomy, Ménétrier's disease.
- Familial risk: 5-10% of cases have a family history of gastric cancer. There is a link between E-cadherin gene mutations and some familial gastric cancers.[6]
- Blood group A (relative risk is 1.2).
- Hypogammaglobulinaemia.

Presentation[7]

- Nonspecific with dyspepsia, weight loss, vomiting, dysphagia and anaemia.
- Early gastric cancer often has symptoms suggesting a benign aetiology. 70% of patients with early gastric cancer only have symptoms of uncomplicated dyspepsia and are not complicated by anaemia, dysphagia, or weight loss.
- Clinical diagnosis is therefore very inaccurate in distinguishing between organic and non-organic disease. All at-risk patients with dyspepsia should be considered for endoscopy.
- The majority of patients present with advanced disease and alarm symptoms such as weight loss, vomiting, anorexia, abdominal pain and anaemia.

- Treatment with antisecretory drugs may delay diagnosis or result in a misdiagnosis on first endoscopy. Proton pump inhibitors (PPIs) may appear to heal malignant ulcers. One study found, however, that such delay does not affect survival or long-term outcome.[8]
- Signs suggesting incurable disease - eg, epigastric mass, hepatomegaly, jaundice, ascites, Troisier's sign (an enlarged left supraclavicular node - Virchow's node), acanthosis nigricans.

Referral guidelines[9]

Urgent suspected cancer pathway (within two weeks)

- Consider offering this to people who have an upper abdominal mass consistent with stomach cancer.

Editor's note
Dr Krishna Vakharia, 16th October 2023 **Suspected cancer: recognition and referral**[9] The National Institute for Health and Care Excellence (NICE) has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

Urgent direct access upper gastrointestinal endoscopy (to be performed within two weeks)

- This should be offered to assess for stomach cancer in people:
  - With dysphagia; **or**
  - Aged 55 and over with weight loss **and** any of the following:
    - Upper abdominal pain.
    - Reflux.
    - Dyspepsia.

Consider offering non-urgent direct access upper gastrointestinal endoscopy to assess for stomach cancer in people with haematemesis.

Consider non-urgent direct access upper gastrointestinal endoscopy to assess for stomach cancer in people aged 55 or over with:

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

Investigations[10] [11]

- Check FBC (possible anaemia) and LFTs.
- Rapid-access video endoscopy and endoscopic biopsy remain the investigations of choice. Biopsies can be taken and small lesions evaluated more fully than is possible with radiological studies. PPI therapy should be ideally withheld until after endoscopy, to avoid misdiagnosis.
- Endoscopic adjuncts such as chromoendoscopy and high resolution endoscopy have been introduced in selected centres although further research is needed as to their role.

- All gastric ulcers should be biopsied (multiple ulcer edge biopsies), as even malignant ulcers may appear to heal on drug treatment. Gastric ulcers should also be followed up, until healing, with repeat biopsy.

Staging[4] [10] [11]

Patients with gastric cancer should undergo careful pre-operative staging to enable appropriate management.

- Spread is local, lymphatic, blood-borne and transcoelomic - eg, to ovaries (Krukenberg's tumour).
- Initial staging assessment should include CT scanning of the thorax and abdomen to determine the presence or absence of metastatic disease. Other modalities such as positron-emission CT and multi-dimensional CT may also be required.
- In the absence of metastatic disease, assessment of operability is preferably made by endoscopic ultrasound.
- Adjuncts to staging include chest radiography, transabdominal ultrasound, magnetic resonance imaging, bronchoscopy and laparoscopy.

Tumour, node, metastasis (TNM) staging

TX, NX or MX indicates 'not assessed'.
T0 - no evidence of primary tumour.
Tis - carcinoma in situ (intraepithelial).
T1 - invades lamina propria or submucosa.
T2 - invades muscularis propria or subserosa (not visceral peritoneum).
T3 - penetrates visceral peritoneum but not adjacent structures.
T4 - invades adjacent structures (spleen, colon, etc).
N0 - no lymph node (LN) metastasis.
N1 - 1-6 lymph nodes.
N2 - 7-15 lymph nodes.
N3 - more than 15 lymph nodes.
M0 - no distant metastasis.
M1 - distant metastasis, in portal lymph node, mesenteric, retroperitoneal or more distant.

Management[4] [11]

- All patients with gastric cancer should be screened for nutritional deficiency and consideration of nutritional support.
- Symptom control includes treatment for pain, nausea, constipation, depression and mouth care.

Surgery

- Endoscopic surgery is the mainstay of treatment for early gastric cancers. Endoscopic mucosal resection (EMR) endoscopic mucosal dissection (ESD), photodynamic therapy (PDT), mucosal ablation using lasers (photothermal), electrocoagulation, argon plasma coagulation (APC) and radiofrequency ablation (RFA) (thermal) have all been employed to remove dysplasia and early cancer.
- Positive results from Japanese studies have enabled endoscopic surgery to be extended to any size of elevated mucosal lesion and ulcerated lesions (<3 cm).

- For early gastric cancer which is not suitable for endoscopic resection, proximal or distal partial resection is appropriate with limited lymphadenectomy (D1).
- The approach to cardia, subcardia and some type II oesophago-gastric junctional cancers can be extended to total gastrectomy or oesophago-gastrectomy, with more extensive lymphadenectomy (D2). There is an increasing interest in laparoscopic surgery for both gastrectomy and lymphadenectomy, although comparison with laparotomies is still in the research stage.
- The distal pancreas and spleen should not be removed as part of a resection for a cancer in the distal two thirds of the stomach. There is increasing evidence that removal of the spleen has an adverse effect on prognosis. The distal pancreas should be removed only when there is direct invasion and still a chance of a curative procedure in patients with carcinoma of the proximal stomach. Resection of the spleen and splenic hilar nodes should only be considered in patients with tumours of the proximal stomach located on the greater curvature/posterior wall of the stomach close to the splenic hilum where the incidence of splenic hilar nodal involvement is likely to be high.

Chemotherapy and radiotherapy [11]

- Perioperative combination chemotherapy has become the standard of care for localised gastric cancer throughout the UK and most of Europe.
- Adjuvant chemotherapy without radiotherapy after surgery is not currently standard procedure in the UK but may be helpful in high-risk patients, especially those who have not had neoadjuvant chemotherapy.
- Postoperative chemoradiotherapy is also not current standard UK practice but may be of benefit in high-risk patients.
- 5-fluorouracil (5-FU) is the most effective chemotherapeutic agent. A combination of 5-FU with other agents is superior to single agent treatment. Various combinations are being explored, of which epirubicin and cisplatin are the most commonly used in the UK.

Editor's note

Dr Krishna Vakharia, 16th October 2023

Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency [12]

NICE has recommended pembrolizumab as an option for treating tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults with:

Advanced or recurrent endometrial cancer that has progressed during or after a platinum-based therapy, who cannot have curative surgery or radiotherapy.

Unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after having one therapy.

Colorectal cancer after fluoropyrimidine combination therapy, only if they cannot have nivolumab with ipilimumab.

Pembrolizumab should be stopped at 2 years of uninterrupted treatment or earlier if the cancer progresses.

Results of indirect trials suggest that people having pembrolizumab live for longer and have longer before their cancer gets worse than people having chemotherapy - though these results are not certain. It is thought that the possibility of its effect on quality and length of life mean that this is an option.

Palliative care [11]

- A multidisciplinary approach to care is essential.
- Palliative care is often needed for obstruction, pain or haemorrhage and involves judicious use of drugs, surgery and radiotherapy.
- Palliative chemotherapy for locally advanced and/or metastatic disease provides quality of life and survival benefit. Various combinations are being explored, including epirubicin, cisplatin and continuous infusion of 5-FU (ECF) and epirubicin with oxaliplatin and capecitabine. Capecitabine is now endorsed by NICE in combination with a 'platin' drug for the palliative treatment of advanced gastric cancer. [13] Pre-operative downstaging of locally advanced disease with chemotherapy may enable resection of previously inoperable cancers.

- Currently there is no indication to recommend second-line chemotherapy. Its role should remain in the context of a clinical trial. Second-line palliative chemotherapy following failure of first-line chemotherapy is still investigational but a combination of folinic acid, 5-FU and oxaliplatin, or docetaxel with or without epirubicin, have demonstrated significant benefits.
- Trastuzumab, in combination with cisplatin and capecitabine or 5-FU, has been endorsed by NICE for use in patients with a certain type of metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (that which has high levels of the antigen HER2) who have not received prior treatment for their metastatic disease.[14]
- Those with distal obstructing tumours may benefit from a subtotal gastrectomy or gastrojejunostomy. Stenting of gastric cardia tumours relieves dysphagia.
- Endoscopic laser therapy may be of help in unresectable obstruction or to control bleeding lesions.
- Blood transfusion may be appropriate for symptomatic anaemia.
- Corticosteroids or megestrol acetate should be considered for management of anorexia.[15]
- Coeliac plexus nerve blocks may be effective in controlling resistant pain.[16]
- Palliative techniques currently in the research stage include photodynamic therapy, argon plasma therapy, ethanol injections and irradiation and stenting combined.

Editor's note

Dr Krishna Vakharia 15th December 2022

Trifluridine-tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more treatments [17]

NICE has recommended trifluridine-tipiracil as an option for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in adults who have had two or more treatment regimens. It has been shown that people using this medication live longer compared to best supportive care.

Dr Krishna Vakharia**, 13th January 2023**

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [18]

Currently there are no curative treatments for HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. NICE has recommended nivolumab with platinum- and fluoropyrimidine-based chemotherapy in these cancers if the tumours express PD-L1 and have a combined positive score (CPS*) of 5 or more. Nivolumab in combination with the above chemotherapy has been shown to extend life.

*CPS is CPS is the ratio of the number of all PD-L1-expressing cells (tumour cells, lymphocytes, macrophages) to the number of all tumour cells.

Prognosis [19]

In the UK:

- More than 45 out of 100 people will survive their cancer for one year or more.
- More than 20 out of 100 people will survive their cancer for five years or more.
- More than 15 out of 100 people will survive their cancer for 10 years or more.

American studies suggest that Asian people have a better prognosis.

Prevention [11] [20]

- A diet with high intakes of fruit and vegetables (at least five servings per day), smoking cessation and reduction of excessive alcohol intake are likely, although not yet proven, to reduce the incidence of gastric cancer. Vitamin supplements are not known to have any effect.
- Control of obesity is likely to be an important factor.
- The usefulness of surveillance endoscopy in Barrett's oesophagus and in the investigation of dyspepsia remains to be confirmed.
- *H. pylori* eradication is likely to be important but its effect on gastro-oesophageal cancer remains to be determined
- COX-2 may be a biomarker for gastric carcinoma and its measurement in gastric biopsies may be a useful secondary preventative strategy. Ironically, aspirin, non-steroidal anti-inflammatory drugs and other COX-2 inhibitors may be beneficial in preventing gastric carcinoma but further research is needed.

Further reading

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