OPEN ACCESS TEXTBOOK OF GENERAL SURGERY

GASTRIC CARCINOMA

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INTRODUCTION

Gastric neoplasms are common, and because they often present late, they arefrequently incurable. The usual histological type is gastric adenocarcinoma, and the major part of this chapter is dedicated to this subtype. Gastrointestinal stromal tumours (GIST) and gastric lymphoma will be dealt with separately.

EPIDEMIOLOGY

Gastric carcinoma is the third commonest cause of cancer death in men, worldwide. The overall incidence of gastric cancer has declined rapidly over the recent few decades, yet there are marked geographic variations of this, with extremely high incidence in Eastern Asia, the Andean regions of South America, and Eastern Europe. Whilst it is not commonly seen throughout Africa, gastric carcinoma is frequently encountered in the in the Western Cape region of South Africa.
Although the peak incidence is in the sixth and seventh decade, gastric carcinoma may be found in the twenties and thirties. The disease is more common in men than women (2:1).

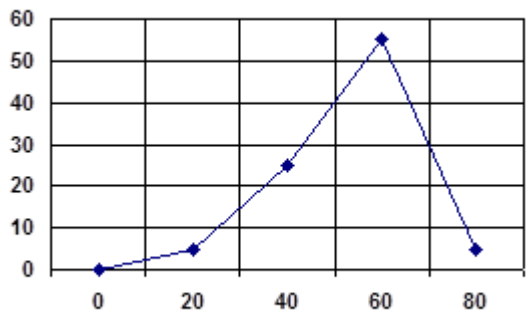

Table 1- *age related incidence of gastric carcinoma*

PREDISPOSING CONDITIONS

Most gastric carcinoma are ***sporadic*** (i.e. they do not have an obvious single predisposing cause or condition) and are thought to arise as a result a variety of risk factors that act over a long period of time to eventually promote carcinogenesis.

The gastric pathology that most facilitates the progression to carcinoma is a state of***chronic atrophic gastritis*** (this may be due to autoimmune disorders, chronic bile reflux, H pylori infection, chronic alcohol use and smoking, poor nutrition).

Atrophic gastritis is associated with an increased risk of both cardia and non-cardia gastric adenocarcinomas with estimates ranging from 3 to 18 times greater than an age-matched population.

The pathogenetic mechanism implicates dietary factors: preserved foods (salted, dried), and lacks of fresh or refrigerated foods are risk factors. Fresh green and orange foods contain anti-oxidants that may prevent some aspects of carcinogenesis. Saltpetre (potassium nitrite, used for meat salting and preservation) is certainly contributory. The intra-gastric milieu of achlorhydriafacilitates bacterial proliferation and conversion of nitrates to nitrosamine products which are further carcinogenic.

Correa's hypothesis is the most accepted theory of how these factors act synchronously to eventually cause a carcinoma. Nutritional defects (absence of fresh food, preservatives, alcohol) damage the gastric mucosa and cause gastritis; cell damage results in defective acid production and the proliferation of bacteria, many of which produce nitrate reductase; dietary nitrate if reduced to nitrite, may

combine with amines to generate nitrosamines, which are known to be carcinogenic. Thus a progression from chronic gastritis to chronic atrophic gastritis, to intestinal metaplasia, dysplasia, and eventually to adenocarcinoma is triggered.

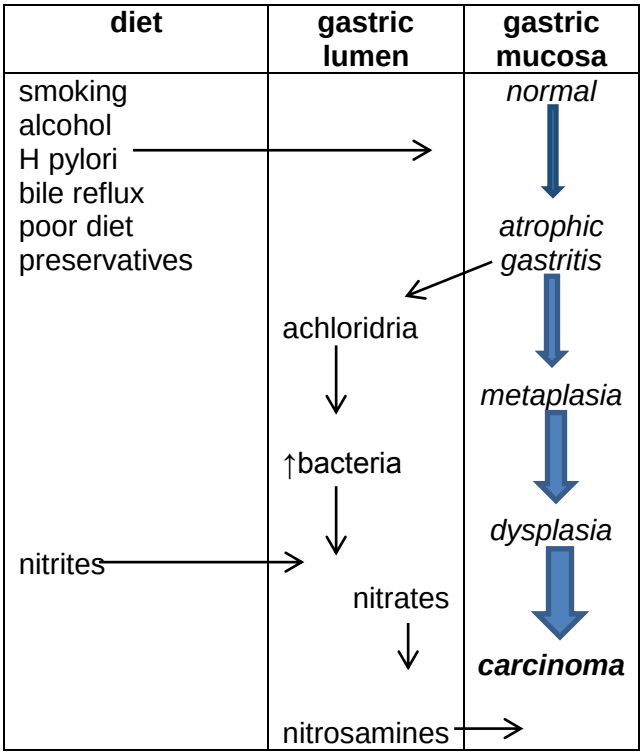

Table2- *Correa's hypothesis of gastric carcinogenesis*

Helicobacter pylori — The WHO's International Agency for Research on Cancer classified H.pylori as a Group 1 or definite carcinogen. It is thought that H.pylori infection triggers inflammation at the corpus mucosa that results in atrophy and intestinal metaplasia. H. pylori infection has been associated with an approximate 6-fold increase in the risk with adenocarcinomas distal to the cardia, including both the intestinal and diffuse types.

A paradox in H. pylori infection is that it can trigger divergent clinical conditions: some patients develop *duodenal ulcer,* some *gastric cancer*, while the majority have *no significant clinical symptoms*. It is thought that the interplay between certain genotypes of H.Pylori (vacAs1-, vacAm1-, and cagA-positive), andspecific host factors in patients who possess cytokine polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C) may explain the pathology processes.

Epstein-Barr virus — Infection with Epstein-Barr virus (EBV) is associated with a number of malignancies, especially nasopharyngeal carcinoma. Studies estimate that between 5 and 10 percent of gastric cancers worldwide are associated with EBV but the exact pathogenetic mechanism is unclear.

Gastric surgery — There is an increased risk of gastric cancer after gastric surgery, with the risk being greatest 15 to 20 years after surgery and then increasing with time. The Billroth II procedure (gastrojejunostomy) carries a higher risk than the Billroth I (gastroduodenostomy). The pathogenesisis linked to reflux of alkaline bile triggering chronic gastritis in the gastric remnant.

Cancer survivors who received ***abdominal irradiation***have an elevated risk of gastric cancer.

Blood group: Individuals of blood group A have an approximately 20 percent excess of gastric cancer than those of group O, B, or AB. They also show a similar increase in the rate of pernicious anaemia.

Familial predisposition: Genetic predisposition to gastric cancer has been repeatedly confirmed, but is not as common or as well defined as in other cancers such as breast or colon. Gastric cancer is occasionally associated with ***cancer syndromes*** such as hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Li-Fraumeni syndrome, hereditary diffuse gastric cancer, and Peutz Jeghers syndrome, but these are all rare.

Hereditary diffuse gastric cancer — hereditary diffuse gastric cancer (HDGC) is an inherited form of diffuse type gastric cancer, a highly invasive tumour that is characterized by late presentation and a poor prognosis. It is also associated with lobular breast cancer in the female carriers of the *E-cadherin gene* mutation. It is inherited as an autosomal dominant trait with high penetrance.

Gastric polyps — most gastric polyps are hyperplastic and not neoplastic, but some may be adenomatous, and have a pre-malignant potential.

Hypertrophic gastropathy - (Ménétrier's disease) has been linked with gastric cancer.

Gastric ulcer — the association between benign gastric ulcers and gastric cancers probably reflects common risk factors. Gastric ulcers are not per se premalignant lesions.

Pernicious anaemia — Pernicious anaemia, a sequel of autoimmune chronic atrophic gastritis, is associated with an increased risk of 2-6 fold of intestinal-type gastric cancer.

PATHOLOGY

Gastric cancer is an adenocarcinoma. Very rarely other pathological diagnoses such as squamous carcinoma or carcinoid may be seen. The most commonly used classification of adenocarcinomas was described by Lauren, and differentiatesthe disease into ***diffuse*** (no acini) and ***intestinal*** (acinar formation) types, some cancers have histological features of both, and are classified as ***mixed.***

	Intestinal	**Diffuse**
macroscopic appearance	*ulceration*	*constricting linitis plastica*
microscopic	*acinar formation*	*no acini*
gastric site	*antrum*	*fundus*
prognosis		*worse*

Table 3- *differences between intestinal and diffuse types of gastric carcinoma*

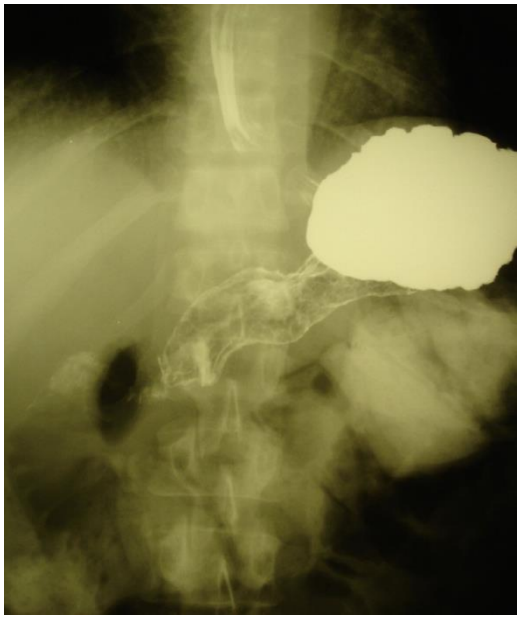

Fig1-*typical appearance of linits plastica, circumferentially narrowing the stomach.*

The intestinal subtype is the commonest form. The disease spreads in the manner of other epithelial malignancies of the gastrointestinal tract: local invasion through and along the intestinal wall into adjacent organs is an early feature, local nodal invasion is common and metastases to the peritoneal cavity occur in advanced cases.

These three modes of spread are described in the TNM classification system. The T stage relates to the depth of invasion through the layers of the gastric wall (mucosa – muscle – serosa – surrounding tissue).
The N stage relates to the number of glands involved: N0 – none; N1- 1-2; N2 – 3-6; N3 - >7. Nodes beyond the

gastric bed and all metastatic disease are classified as M1. Various TNM classification combinations are further grouped into stages that relate to prognosis.

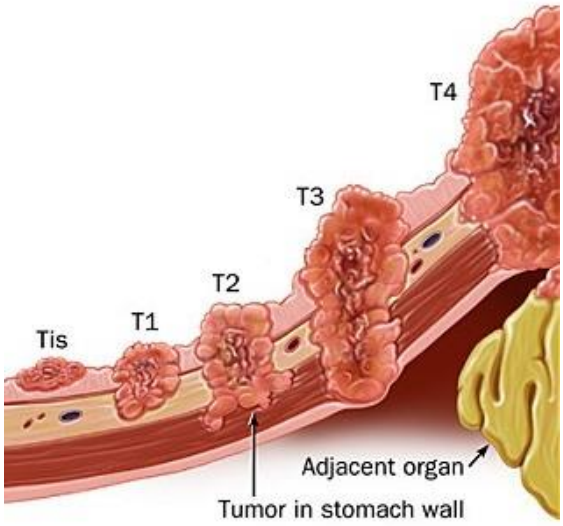

Fig2- *T staging of gastric carcinoma (https://gi.jhsps.org/GDL_Disease.aspx)*

PRESENTATION

The majority of patients with gastric cancer are symptomatic and already have advanced incurable disease at the time of presentation. At diagnosis, approximately 50% have loco regionally advanced disease and only a minority of these can undergo a potentially curative resection. Surgically curable early gastric cancers are uncommon.

clinical presentation of gastric carcinoma	
dyspepsia	60%
local complications *haemorrhage* *obstruction* *perforation*	30%
insidious *loss of weight* *anaemia* *metastases*	10%

Table 4- *Presentation of gastric carcinoma*

The early symptoms of gastric carcinoma are similar to those of benign conditions of the foregut (stomach, duodenum, biliary apparatus, pancreas and upper small bowel).Such symptoms may be collectively grouped as ***dyspepsia***: anorexia, fullness, discomfort, pain, nausea, vomiting, etc., and the *symptoms of peptic ulcer and gastric carcinoma are notoriously indistinguishable.*

The vast majority of cases of gastric carcinoma have had several courses of medical treatment for presumed peptic ulceration before the diagnosis was made, and the delay before definitive treatment usually has been an unfortunate 6-12 months.

Differential diagnosis of dyspepsia	
functional (non ulcer) dyspepsia **diagnosis by exclusion*	65%
peptic ulcer disease gastritis	10%
gastro-oesophageal reflux oesophagitis	10%
drug side effects	5%
biliary disease	2-3%
gastric carcinoma	1-2%
other *pancreatic carcinoma/ peritoneal carcinomatosis/ ovarian pathology/ retroperitoneal sarcoma/ lymphoma*	1-2%

Table 5- *Differential diagnosis of dyspepsia*

Whilst the majority of patients with dyspepsia will not have ominous pathology, it is important to remember that some may have gastric cancer or other GIT malignancies. Dyspepsia is significant when the symptoms have been present for more than two weeks (and dietary indiscretions will have resolved). Such dyspepsia requires thorough investigation. A trial of medical treatment without investigation and appropriate follow up is inappropriate as gastric carcinoma may respond to medication, by placebo effect or by the healing of peri-carcinomatous peptic digestion.

The complications of gastric carcinoma include ***haemorrhage*** (usually causing anaemia rather than an overt bleed), ***gastric outlet obstruction***, and ***perforation***.

Causes of gastric outlet obstruction	
gastric carcinoma	35%
peptic ulcer	35%
pancreatic pathology	20%
carcinoma or pseudocyst	
corrosive stricture	5%
rarities	5%
adenopathy/volvulus/ bezoars	

Table6- *Gastric outlet obstruction*

The ***insidious presentations*** are with unexplained weight loss, anaemia, jaundice, ascites or metastatic malignant disease. Most of these last presentations reflect advanced and incurable disease; cure is obtained when the clinician is aware that the dyspeptic patient could possibly have gastric carcinoma, and appropriate investigations are performed.

Dysphagia is also a common presenting symptom in patients with cancers arising in the proximal stomachor at the oesophagogastric junction.

Clinical signs are uncommon, and usually a mark of advanced disease. In some patients it may be possible to palpate an epigastric mass due to tumour bulk, supraclavicular adenopathy (Virchow-Trosier node) is a mark of lymphatic spread; ascites and pelvic masses (Krukenberg ovarian tumours in women or Blumer's shelf in men) occur with pelvic peritoneal metastases.

Paraneoplastic manifestations are very uncommon, but may include the sudden appearance of diffuse seborrheic keratoses (sign of Leser-Trelat) or acanthosis nigricans, which is characterized by velvety and darkly pigmented patches on skin folds. Neither finding is specific for gastric cancer.

DIAGNOSIS AND STAGING

A prompt diagnostic evaluation should be commenced when gastric cancer is suspected.

The primary investigation is ***endoscopy***. The ability to perform biopsy during endoscopy adds to its clinical utility. All gastric ulceration should be biopsied, even if it appears "benign" to the eye of the endoscopist. A single biopsy has 70% sensitivity for diagnosing an existing gastric cancer, while performing seven biopsies from the ulcer margin and base increases the sensitivity to greater than 98%.

Once the diagnosis is confirmed, it is essential to thoroughly evaluate the patient and the extent of the disease.

Decision making with gastric carcinoma

1. Confirm histological diagnosis with endoscopic biopsy.
2. Metastatic screen *(CXR, liver profile and ultrasound/ CT)*
3. Assess extent (barium meal/ CT in certain proximal lesions/ staging laparoscopy/ endoscopic US)
4. Assess fitness for surgery.

Surgery appropriate ± 70%	**Surgery inappropriate ± 30%**
Irresectable /obstructed: *bypass/ stent*	THE DISEASE *Incurable*: metastases, ascites, extent
Resectable	
Palliative	
Curative (T1-3, N0-1, M0)	THE PATIENT Elderly, compromised, refusal.

Clinical staging directs the initial approach to therapy: patients who appear to have loco regional disease only are potentially curable; they should be referred for multidisciplinary evaluation to identify the best treatment strategy.

Patients with advanced stage IV disease (metastases) are usually referred for palliative therapy depending on their symptoms and functional status.

SURGICAL MANAGEMENT

Resection offers the best chance for long-term survival for patients with localized gastric cancer, and is the cornerstone of therapy. The key problem is that overall only 10-20% has potentially curable disease at presentation.

Awareness of the diagnosis, appropriate investigations for upper GIT symptoms, and early referral are essential.

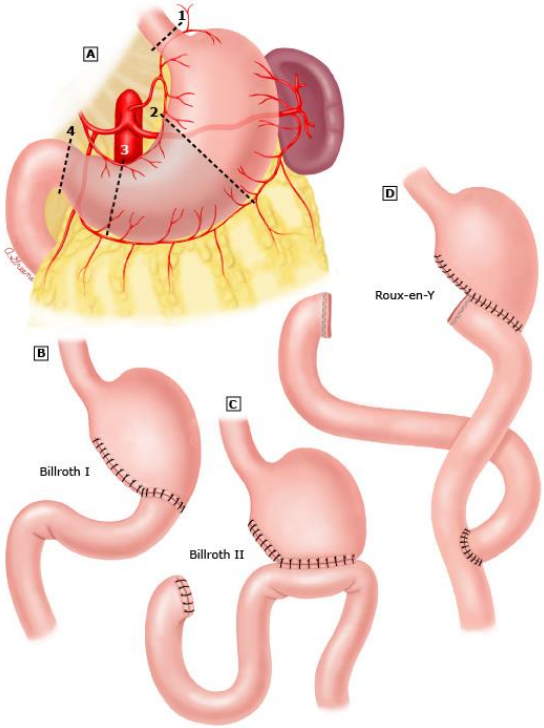

Fig 3- *Distal (partial) gastrectomy is performed by removing the distal portion of the stomach. Gastrointestinal continuity can be restored using (B) known as a Billroth I (stomach to the duodenum)/ Billroth II (C) (loop of proximal jejunum to create an end-to-side gastrojejunostomy)/ or Roux-en-Y gastrojejunostomy (C). (UpToDate-Surgical management of invasive gastric cancer-2014)*

Surgical treatment for localized disease: Complete surgical eradication of a gastric tumour with resection of adjacent lymph nodes represents the best chance for long-term survival. A laparotomy with curative intent should be undertaken unless there is unequivocal evidence of disseminated disease, major vascular invasion, or there are medical contraindications to surgery.

Lesions of the distal half of the stomach are managed by *distal gastrectomy and gastrojejunal anastomosis* (Billroth II). Other reconstructive techniques are occasionally used (Billroth I or Roux-en-Y)(Fig 3).

More extensive lesions or those involving of the proximal half of the stomach are managedby *total gastrectomy and oesophagojejunal anastomosis*(Fig 4).

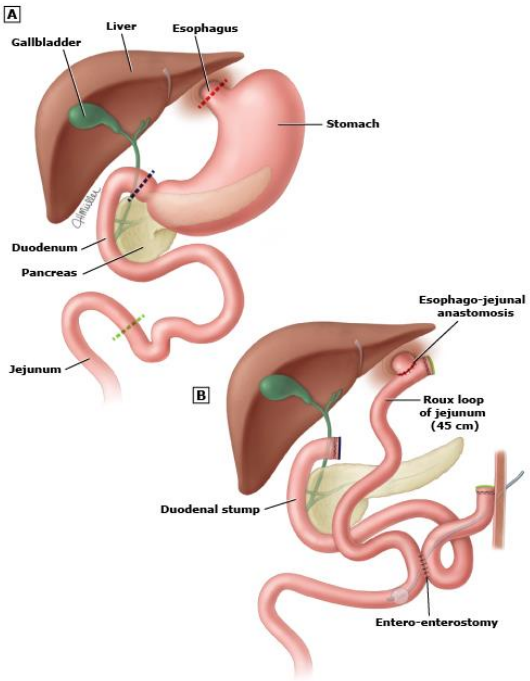

Fig 4- *Total gastrectomy with oesophagojejunal reconstruction. (UpToDate-Surgical management of invasive gastric cancer-2014)*

The extent of *lymph node dissection* is a subject of surgical controversy, but extended radical lymphadenectomy is probably of little benefit.

Surgery for incurable/ metastatic disease: Irresectable, obstructed lesions may be surgically palliated: in the distal stomach a bypass may be possible, and inselected cases with incurable disease, surgery may palliate the complications of haemorrhage, obstruction or perforation.

ADJUVANT/ NEOADJUVANT THERAPY

The poor long-term survival rates after surgery alone have led to the exploration of a variety of adjuvant (postoperative) and neoadjuvant (preoperative) strategies. Multidisciplinary preoperative evaluation is preferable to fine tune this decision. The location of the cancer (i.e. antrum/ body or fundus) the local depth of penetration (i.e. the T stage), and the presenting symptoms determine what strategy is to be used. Most oesophago-gastric (and cardia) cancers can be treated like oesophageal adenocarcinomas, using preoperative chemo radiotherapy.

For patients with non-cardia gastric cancer there is increasing use of adjuvant chemo radiotherapy, or perioperative (preoperative plus postoperative) chemotherapy.
Patients with intolerable symptoms (complete obstruction, bleeding or perforation) may need to undergo surgery primarily.

PALLIATION

As the majority of patients present late, the bulk of management centres on correctly chosen palliative treatment.

The aim of any palliative regime is to deal with the patients symptoms, and to improve them in the least harmful way. In this context the natural desire to intervene and “do something” has to be tempered with realist expectations. If the patient is asymptomatic there is little role for active intervention.

Cytotoxic chemotherapy has a demonstrable benefit in a subgroup of patients with metastatic disease, but is not very effective for symptoms such nausea, pain, obstruction, perforation, or bleeding from a locally advanced or locally recurrent primary tumour. It is an option in patients who are fit enough to tolerate it, and does not offer cure.

Patients with obstructive symptoms are best managed with endoscopic placement of a stent.Stenting has comparable success as surgical palliation (with a clinical improvement of 90%) but is cheaper and associated with less morbidity.

Radiotherapy can control pain and (occasionally) reduce bleeding from an irresectable tumour.

Psychological, sociological and medical support is very important. When recurrent or incurable disease is present, patients should be counselled together with their families and provision made for continuing support. Frequent short admissions to hospital for transfusion or rehydration may be necessary. Pain is not usually a major feature, but when present may be treated with opiates.

PROGNOSIS

The long term prognosis is governed by the tumour stage at presentation. Since the majority of patients present late (Stage III/ IV) the overall prospect of cure is low. Those patients diagnosed with early gastric carcinoma can expect a good chance of long term survival.

Stage	5 year survival
I a b	78% 58%
II	34%
III a b	20% 8%
IV	7%

Table7- *Five-year survival rates for gastric adenocarcinoma, as reported in the population-based US National Cancer Data Base.*

GASTROINTESTINAL STROMAL TUMOURS

Gastrointestinal Stromal Tumours (GIST) are most often located in the stomach, and for this reason they are discussed in this chapter, but they may occur at other GIT sites, such as the proximal small intestine, the omentum, mesentery, and peritoneum.

They are sub-epithelial neoplasms, and as such they only cause symptoms when they reach a large enough size to compress adjacent structures, ulcerate and bleed, or become clinically palpable.

The clinical behaviour of GISTs is highly variable; the main prognostic determinants are tumour size, mitotic rate, and tumour location. Small (<2cm) GISTs are of little clinical relevance, yet larger, high grade lesions can metastasize and be fatal.

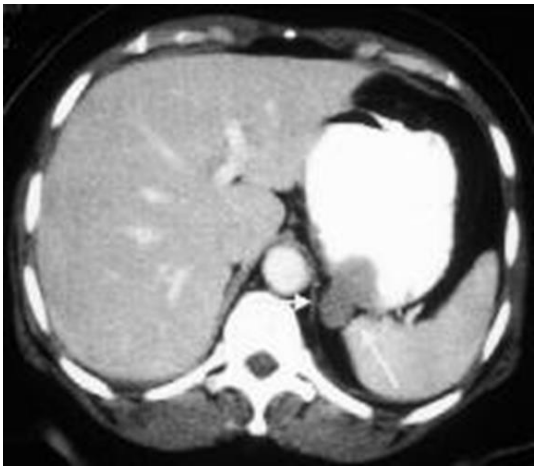

Fig 5- *CT image of a GIST in the fundus of the stomach*

The primary management is surgical, requiring a resection of the part of the stomach involved by the tumour. This may vary from a limited wedge excision in early cases, to total gastrectomy.

A striking feature of these tumours is that over 95% of GISTs express the CD117 antigen, part of the KIT transmembrane receptor tyrosine kinase (RTK), a product of the *c-KIT proto-oncogene*. As a result of this feature they are responsive to treatment with the molecular targeted therapy Imatinib, designed to block tyrosine kinase receptor. Systemic therapy can be highly effective in patients with malignant and metastatic GISTs.

GASTRIC LYMPHOMA

Primary lymphomas of the GIT tract are uncommon. The vast majority are non-Hodgkin lymphomas, and the usual site of involvement is the stomach (70%) followed by the small bowel, colon, rectum, and oesophagus.

Gastric lymphoma presents with nonspecific dyspeptic upper GIT symptoms,or GI bleeding. At endoscopy they may appear similar to adenocarcinoma of the stomach, so an adequate biopsy is fundamental to confirm the diagnosis.

There is a strong association between gastric lymphoma and certain types of H.pylori infection, and early stage, low grade lymphomas will respond to H.Pylori eradication alone.

The majority of gastric lymphomas coming to surgical attention, however, will be aggressive, high grade lymphomas- these are usually treated with systemic CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)

chemotherapy, with good expectation of response. Operative surgery has a limited role in their management.