Gastric Tumors: an overview

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Identity

Note

The vast majority of both benign and malignant tumours of the stomach are of epithelial origin, with mesenchymal and neuroendocrine tumours being much less common. Gastric adenocarcinoma comprises in excess of 95% of malignant neoplasms of the stomach, and is thus the focus of this overview. Primary gastric lymphoma is the second commonest malignancy affecting the stomach with gastrointestinal stromal tumours (GISTs) and rare tumours, such as carcinoids, accounting for the remainder of cases.

Classification

Benign Tumours
Neoplastic
- Epithelial adenomas
- Fundic gland polyps
- GISTs
- Lipomas
- Leiomyomas
- Neural tumours (e.g. Schwannomas)
Non-Neoplastic
- Hyperplastic polyps
- Inflammatory fibroid polyps
- Hamartomatous polyps
  - Juvenile
  - Peutz-Jegher's Syndrome
  - Cowden’s Syndrome

Malignant Tumours
- Adenocarcinoma
- Primary gastric lymphoma
- GISTs
- Metastatic deposits
- Carcinoids

- Rare tumours
  - e.g. Sarcomas, neuroendocrine carcinoma,
  primary squamous cell carcinoma and
  adenoacanthomas

Clinics and pathology

Disease

Benign Gastric Polyps

Note

Benign gastric polyps are found incidentally in 2-3% of upper gastrointestinal endoscopies. Their incidence increases with patient age. Small polyps are almost always asymptomatic. Larger polyps may bleed due to erosions or ulceration. Very large distal polyps may produce obstructive symptoms.

Small hyperplastic and fundic gland polyps are relatively common. They are generally regarded as being of no significance although multiple fundic gland polyps with evidence of dysplasia can occur in familial adenomatous polyposis (FAP). Fundic gland polyps and, to a lesser extent, hyperplastic polyps, occur with increased frequency in patients on long-term proton pump inhibitor therapy.

Inflammatory fibroid polyps (IFPs) are uncommon solitary lesions that arise in the distal stomach. They usually originate submucosally however the overlying mucosa commonly develops erosions or ulceration. IFPs are felt to be reactive in nature and are composed of a mixture of proliferating fibroblasts, blood vessels and inflammatory cells. Eosinophils are often present. Helicobacter pylori has been implicated in the etiology of IFPs as have chemical and mechanical irritants.

Adenomatous polyps in the stomach usually arise against a background of chronic atrophic gastritis with intestinal metaplasia although they too can occur in FAP. Gastric adenomata are composed of dysplastic...
epithelium with tubular and/or villous architecture. Polyp size and the grade of dysplasia are felt to be predictors of progression to carcinoma. Because gastric adenomata, like those in the colon, represent a premalignant condition, excision (usually possible endoscopically) is the treatment of choice.

**Disease**

Gastric adenocarcinoma

**Etiology**

*Helicobacter pylori*

H. pylori is the single most important etiological agent in the pathogenesis of gastric cancer. Numerous epidemiological studies have demonstrated an association between serological evidence of H. pylori infection and gastric cancer risk. The conclusion of several meta-analyses of these data is that chronic H. pylori infection confers around a two-fold increase in the risk of developing gastric cancer. H. pylori strains expressing the cytotoxin-associated gene A antigen (CagA) are associated with a further two-fold increase in gastric cancer risk. The association with H. pylori appears strongest for non-cardia gastric cancer, but applies to both intestinal and diffuse histological subtypes.

With respect to cancer of the gastric cardia, recent data suggest that there are two distinct etiological subtypes: one arising in the context of severe atrophic gastritis and akin to non-cardia cancer, and a second arising in non-atrophic mucosa, associated with gastro-oesophageal reflux disease and resembling oesophageal adenocarcinoma.

**Host Genetics**

Individual differences in the inflammatory response to H. pylori infection, as determined by host genetic polymorphisms, may predispose to the development of a gastric cancer phenotype. Pro-inflammatory polymorphisms have been described in the interleukin-1 gene cluster, and tumour necrosis factor-alpha, interleukin-10, interleukin-8, and interferon-gamma genes. Having an increasing number of such pro-inflammatory genetic polymorphisms confers an increased gastric cancer risk for an H. pylori-infected individual.

**Diet and Smoking**

It has been postulated that diets rich in fruit and vegetables are associated with a reduced risk of gastric cancer. To date, data from large prospective studies do not bear this out. Similarly, there are conflicting data regarding the increased risk associated with dietary salt and nitroso compound intake. There is a dose-dependent relationship between smoking and gastric cancer. It is estimated that over 17% of gastric cancers in Europe are directly attributable to cigarette smoking.

**Epidemiology**

Gastric cancer is the second most common cause of cancer-related death globally. Although the incidence of gastric cancer has fallen significantly in most countries over the past 70 years, the global incidence is predicted to rise as a result of population growth. There are marked geographical variations in the incidence of gastric cancer. The highest incidence is found in Eastern Asia, Eastern Europe and South America. In all populations studied thus far, there is a male preponderance in gastric cancer incidence with an average male to female ratio of 2:1.

**Clinics**

Early gastric cancer is most likely asymptomatic in most patients, or may produce non-specific dyspeptic symptoms. Alarm symptoms such as anorexia, weight loss, dysphagia or gastrointestinal haemorrhage usually betray advanced disease.

**Pathology**

Historically, gastric cancers were classified according to the Laurén classification as being of either intestinal or diffuse histological type. The pathogenesis of intestinal type gastric cancer has been defined as following a pathway from atrophic gastritis, through intestinal metaplasia and dysplasia, to frank malignancy. No such pathogenic sequence of progression exists for diffuse type gastric cancer. More recently, gastric cancers have been classified anatomically as either cardia or non-cardia in origin.

**Treatment**

Resection with curative intent is the only treatment that will result in long-term survival from gastric adenocarcinoma. Palliative and neo-adjuvant chemotherapy improve survival in selected patients.

**Prognosis**

In Western countries, 90% of gastric cancers are inoperable at presentation and thus 5-year survival rates are low. In Japan, where population-based screening takes place, 5-year survival exceeds 50%.

**Disease**

Primary gastric lymphoma

**Note**

The vast majority of primary lymphomas arising in the stomach are of non-Hodgkin's B-cell type.
Recent series have demonstrated that low-grade marginal zone lymphomas of mucosa-associated lymphoid tissue (or MALT lymphomas) account for over 50% of cases of primary gastric lymphoma. Historically the predominant histological type was diffuse large B-cell lymphoma (DLBCL).

Etiology
The gastric mucosa is normally devoid of lymphoid tissue. H. pylori is implicated as an etiological agent in over 92% of cases of gastric MALT lymphoma. Chronic H. pylori infection results in a lymphoid follicular gastritis and so to the acquisition of gastric MALT. MALT lymphomagenesis is thought to be dependent on clonal expansion driven by H. pylori antigenic stimulation. The mechanisms involved in the transformation of low-grade gastric MALT lymphoma to high grade DLBCL are not well understood.

Clinics
Patients with primary gastric lymphoma may present with non-specific dyspeptic symptoms, early satiety, or evidence of gastrointestinal haemorrhage due to ulcerating disease. Systemic symptoms may be present in advanced stage disease.

Pathology
MALT lymphomas display cellular heterogeneity. Lymphoid follicles may be present with tumour cells located in the marginal zone. Lymphoepithelial lesions are typical in gastric MALT lymphoma. Staging, using a modified Ann Arbor system, can be achieved using endoscopic ultrasonography.

Treatment
Eradication of H. pylori using standard antibiotic regimens results in complete response in around 75% of patients with limited stage MALT lymphoma. Patients who fail to respond to antibiotic therapy, are H. pylori negative, or have nodal disease may be treated in a similar manner to other lymphomas with the use of systemic chemotherapy (e.g. CHOP), immunotherapy (e.g. Rituximab) and/or radiotherapy for localized disease. There is no evidence that surgery is superior to medical therapy alone although surgical intervention may be appropriate in specific scenarios such as gastric outlet obstruction.

Prognosis
The response of low grade MALT lymphoma to H. pylori eradication is predicted by stage. Complete response is achieved in all patients where disease is limited to the gastric mucosa or submucosa. Complete response rates fall where disease extends to the muscularis or serosa, and no patients with nodal disease achieve complete response with H. pylori eradication alone.

The presence of the cytogenetic aberration t(11;18)(q21;q21) predicts lack of response to H. pylori eradication and is found frequently in H. pylori negative MALT lymphomas. Strong nuclear expression of BCL10, associated with t(1;14)(p22;q32), is also associated with lack of response to antibiotic therapy.

Disease
Gastrointestinal Stromal Tumours

Note
Gastrintestinal stromal tumours (GISTs) are the commonest mesenchymal tumours of the GI tract. They are defined by the expression of CD117 (c-KIT), a receptor tyrosine kinase. Gain-of-function mutations in KIT or the platelet derived growth factor alpha gene PDGFA are critical to GIST tumourigenesis. Around 60% of GISTs arise in the stomach and approximately 25% of gastric GISTs display clinically malignant behaviour. GISTs, however, account for only 1-3% of malignant tumours of the stomach.
Most GISTs are sporadic although a small percentage occur in the context of neurofibromatosis type 1 and the very rare Carney triad (in association with functioning extra-adrenal paragangliomas and pulmonary chondromas).

**Clinics**

Small GISTs may be asymptomatic or found incidentally at upper GI endoscopy. Acute or chronic gastrointestinal haemorrhage, due to ulceration of the gastric mucosa superficial to a GIST, is the commonest clinical presentation. Large GISTs may produce symptoms of gastric outlet obstruction or present with pain/dyspepsia, early satiety and nausea.

**Pathology**

Gastric GISTs are highly cellular and tend to be of either spindle cell or epithelioid subtypes. The distinction between benign and malignant GISTs is not clear-cut, rather they display a spectrum of biological behaviour. Mitotic index, size and the use of immunohistochemical proliferation markers may give an indication of the malignant potential of a GIST.

**Treatment**

Surgical resection is the treatment of choice for GISTs. There are favourable trial data supporting the use of the tyrosine kinase inhibitor, Imatinib, in patients with metastatic or unresectable GISTs.

**Disease**

Gastric Carcinoid

**Note**

Gastric carcinoid tumours are rare, comprising only 0.5% of gastric tumours. They arise in the oxyntic mucosa of the gastric corpus and fundus and are comprised of non-functioning enterochromaffin-like cells. Gastric carcinoid tumours may be sporadic or can occur in the context of autoimmune atrophic gastritis, Zollinger-Ellison syndrome and in the MEN-1 syndrome. Carcinoid tumours over 2cm in size are associated with an increased risk of lymphovascular invasion and metastasis, and resection is recommended.

**Genetics**

**Note**

Around 10-15% of gastric cancers are familial. Hereditary diffuse gastric cancer (HDGC) is a highly penetrant autosomal dominant condition with an average age at diagnosis of 38 years. Around one third of families have inactivating mutations in the E-cadherin gene. Increased gastric cancer risk is observed in a number of dominantly-inherited cancer predisposition syndromes including hereditary nonpolyposis colon cancer (HNPPCC), familial adenomatous polyposis (FAP), Peutz-Jegher's syndrome and in BRCA2 mutation carriers.

**Cytogenetics**

**Cytogenetics Morphological**

Numerous abnormalities of chromosome structure and number have been reported in gastric cancer series although no specific aberration has yet been identified. Those chromosomes most commonly involved in simple numerical aberrations include X, Y, 1, 7, 8, 9, 17 and 20. Polysomy for chromosome 17 has been reported to be associated with lymphovascular invasion and nodal metastases.

Conventional cytogenetic analysis of 15 gastric cancers using G-banding revealed structural aberrations most commonly involving chromosomes 1, 11, 14, 7, 17, 6, 8 and 13. The aberration add(11)(p15) was found in five of the cancers analysed.

Multicolour spectral karyotyping has been employed to identify recurrent chromosomal rearrangements in gastric cancer cell lines. Chromosome 8 was most commonly involved in rearrangements. Recurrent translocations, frequently involving known oncogene and tumour-suppressor gene loci, were identified with breakpoints most frequently occurring at bands 8q24 and 11q13.

**Cytogenetics Molecular**

Comparative genomic hybridization has been used to screen for abnormalities of copy number in gastric cancers. In a study of 62 gastric adenocarcinomas, and 6 cell lines, 84% of tumours and all of the cell lines showed changes in DNA copy number. Specific patterns of allelic gains and losses appeared to correlate with different histopathological and disease-related features, such as metastases.

Loss of heterozygosity (LOH) studies in gastric adenocarcinomas have shown high LOH at chromosome arms 1p, 3p, 4p, 5q, 7p, 8p, 9p, 12q, 13q, 17p, 18q and 22q. The intratumoural distribution of LOH between early and advanced gastric cancer has been compared, and suggests that multiple losses occur as an early event in tumorigenesis with a few sporadic losses occurring later in disease progression.

**Genes involved and proteins**

**CDH1**

**Location**

16q22.1

**Protein**

CDH1 encodes E-cadherin, a member of the cadherin superfamiy of calcium-dependent cell adhesion molecules. Downregulation of E-cadherin is observed in a number of epithelial-derived human cancers and promotes invasion through loss of epithelial cell-cell adhesion.

**Germline mutations**

Approximately 30-40% of HDGC kindred harbour germ line mutations in CDH1.
Somatic mutations
Somatic mutations are found in more than 50% of diffuse type gastric cancers but are not found in the intestinal histological type. There is a significant rate of LOH for CDH1 in sporadic gastric cancers (SGCs) of both histological types. Downregulation via promoter hypermethylation, along with mechanisms acting at transcriptional and post-transcriptional level, may act as the "second hit" in both inherited and sporadic diffuse cancers.

**C-MYC**

*Location* 8q24.12-q24.13

*Protein*
The C-MYC proto-oncogene encodes a transcription factor involved in activation of a number of genes involved in cell proliferation.

*Somatic mutations*
C-MYC amplification/overexpression has been described in around 16% of SGCs. Allelic gain through chromosome 8 polysomy has been suggested as an important mechanism of C-MYC amplification in SGCs. C-MYC locus amplification is associated with increased aggressiveness and metastasis in intestinal-type tumours.

**C-ERBB2**

*Location* 17q21.1

*Protein*
C-ERBB2 (HER2) encodes p185, a tyrosine kinase cell surface receptor structurally similar to human epidermal growth factor receptor (EGFR). The protein conformation of p185 permanently resembles the ligand-bound state of EGFR. p185 is a potential target for trastuzumab (Herceptin) therapy.

*Somatic mutations*
C-ERBB2 is amplified/overexpressed in 8-30% of gastric cancers. C-ERBB2 expression is more common in intestinal type tumours and is a marker of invasion and metastasis. Somatic mutations within the kinase domain have been reported in gastric cancers as well as other solid tumours.

**C-MET**

*Location* 7q31

*Protein*
The MET proto-oncogene encodes a transmembrane high affinity receptor for hepatocyte growth hormone.

*Germinatal mutations*
A small number of case reports exist of germ line mutations in MET predisposing to gastric cancer.

*Somatic mutations*
Overexpression of C-MET has been reported in both histological subtypes of gastric cancer and is associated with poor prognostic features. The H. pylori CagA protein appears to interact with the MET protein leading to activation.

**APC**

*Location* 5q21-q22

*Protein*
The APC tumour suppressor protein is a key component of the WNT / Beta-catenin signalling pathway.

*Germinatal mutations*
Gastric fundic gland polyps are observed as an extracolonic feature of FAP. Occasional malignant transformation has been reported.

*Somatic mutations*
Whilst somatic APC mutations are common in gastric cancers, their significance with regards to tumorigenesis remains unclear. It has been postulated that APC mutations play a role in adenoma formation and dysplasia, rather than the promotion of malignant progression.

**TP53**

*Location* 17p13.1

*Protein*
The transcription factor p53 plays a critical role in cell cycle arrest, senescence, DNA repair and apoptosis.

*Germinatal mutations*
Although not one of the classical Li-Fraumeni-associated neoplasms, early onset gastric cancers occur uncommonly in Li-Fraumeni Syndrome (LFS) kindred. Case reports exist of familial gastric cancer in Japanese and Korean families with germ line p53 mutations. It has been suggested that LFS may give rise familial clustering of gastric cancer in regions with high gastric cancer incidence.

*Somatic mutations*
Loss of functional p53 has been reported in virtually all human cancers including gastric cancers. Data on the significance of p53 mutations in SGC development, progression, and prognosis are conflicting.

**FGFR2**

*Location* 10q26

*Protein*
K-SAM encodes the fibroblast growth factor receptor 2.

*Somatic mutations*
The oncogene K-SAM is amplified/overexpressed in approximately 50% of diffuse type gastric cancers but not in the intestinal histological type.

**COX2**

*Location* 1q25.2-q25.3
**COX2** is upregulated in 49-83% of gastric cancers. COX2 expression is particularly high in early gastric cancers suggesting that it may play an important role in early events in tumorigenesis. There is conflicting evidence on the association between H. pylori and the induction of COX2 in gastric cancer.

**Protein**

Cyclo-oxygenase 2 is an inducible enzyme responsible for regulating prostaglandin biosynthesis. COX2 activity is normally undetectable in gastric mucosa.

**RUNX3**

**Location**

1p36

**Protein**

The runt-related transcription factor 3 acts as a tumour suppressor protein.

**Somatic mutations**

Silencing of RUNX3 has been reported in up to 60% of gastric cancers and appears to be effected through hypermethylation of CpG islands within the exon 1 region. Hemizygous deletion of RUNX3 is observed in around 30% of gastric cancers, whilst mutations and small deletions seem to be rare.

**PTEN**

**Location**

10q23.31

**Protein**

The "phosphate and tensin homolog" acts as a tumour suppressor. The protein is involved in regulation of cell cycle progression in the G1 phase. Inactivation of PTEN is observed in multiple advanced cancers and cancer cell lines.

**Germinal mutations**

Gastric hyperplastic polyps are a recognised feature of Cowden's syndrome although these are generally considered non-neoplastic.

**Somatic mutations**

LOH for PTEN has been reported as 20% for early gastric cancers compared to 30% for advanced cancers. The mutation rate in advanced gastric cancers is around 10%.

**DNA repair**

**Note**

3p21.3 (MLH1), 2p22-p21 (MSH2), 2p16 (MSH6), 5q11-q12 (MSH3), 14q24.3 (MLH3), 3q21-q22 (MBD4).

**Protein**

DNA mismatch repair (MMR) enzymes.

**Germinal mutations**

Gastric adenocarcinoma is a recognised part of the hereditary nonpolyposis colon cancer (HNPCC) spectrum of tumours. Dominantly inherited germ line mutations in MLH1 and MSH2 account for 90% of cases of HNPCC. HNPCC confers a 5% lifetime risk of gastric cancer.

**Somatic mutations**

Micosatellite instability (MSI) is the hallmark of defects in the MMR system. Around 15% of SGCs show MSI, most frequently due to hypermethylation of the MLH1 promoter. Recent data suggest that mutations in known MMR genes in SGCs are uncommon and likely arise as a result of the mutator phenotype, rather than cause it.

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