Pathology of oesophageal and gastric tumours

Heike I. Grabsch

Oesophagus

Introduction

Patients with malignant tumours of the oesophagus most commonly present clinically at an advanced disease stage with strictures, plaque-like lesions, polypoid masses protruding into the lumen, diffuse thickening of the mucosa and wall or deeply penetrating ulcers. Oesophageal neoplasms can be broadly divided into epithelial and mesenchymal subtypes according to the cell of origin. Whilst epithelial neoplasms are much more common and can be recognised endoscopically due to mucosal irregularities, mesenchymal neoplasms are usually located in the submucosa with a normal overlying mucosa.

Precursor lesions of squamous cell cancers will be discussed in this chapter, together with their histopathological features as well as relevant molecular pathology. However, precursor lesions of oesophageal adenocarcinoma and molecular pathology of oesophageal adenocarcinoma are only briefly mentioned here as they are covered in depth in Chapter 15. Lymphoma, melanoma, choriocarcinoma and secondary tumours (metastases) of the oesophagus are not discussed here.

Benign tumours and tumour-like lesions of the oesophagus and the gastro-oesophageal junction

Benign oesophageal tumours and tumour-like lesions constitute about 1% of all clinically symptomatic oesophageal lesions, with dysphagia being the most common symptom. Bleeding due to a benign oesophageal tumour is rare and mostly related to secondary ulceration of the luminal surface.

Leiomyoma is a smooth muscle (e.g. mesenchymal) tumour first described by Virchow in 1867 and surgically resected for the first time by Sauerbruch in 1932. Leiomyomas account for more than 50% of all benign tumours of the oesophagus and are twice as frequent in males as in females. Leiomyomas most commonly arise from the muscularis propria and are typically located in the distal or middle oesophagus. Most are less than 3 cm in size, form a firm white-greyish mass and may be calcified. In contrast to gastrointestinal stromal tumours, leiomyomas are immunoreactive for desmin and smooth muscle actin and negative for c-KIT (CD117) and DOG1 (Discovered On GIST 1).

Developmental cysts and congenital oesophageal duplications are the second most common benign lesions of the oesophagus. Inclusion cysts are located within the oesophageal wall at the height of the tracheal bifurcation and may cause compression of the neighbouring respiratory tract. Duplication cysts share the muscularis propria with the oesophagus and can be lined by oesophageal or gastric mucosa. Although they are located extramurally and usually do not communicate with the oesophageal lumen, symptoms and complications may occur due to ulceration, haemorrhage and perforation requiring surgical intervention.

Fibrovascular polyps are the commonest intraluminal benign tumours of the oesophagus, representing 12% of all benign oesophageal tumours. They are usually located in the cervical oesophagus and are often 7 cm or longer when they become symptomatic. To prevent
possible complications such as regurgitation or even fatal asphyxia, fibrovascular polyps are usually surgically removed.

**Squamous cell papillomas** are rare (less than 1% of all benign oesophageal tumours) but nevertheless represent the most frequent benign epithelial tumour of the oesophagus. They are most commonly located in the lower third of the oesophagus, are exophytic with a warty surface, sessile or partly pedunculated, well demarcated and measure usually less than 5 mm in diameter. Related to its endoscopic/macroscopic appearance, the differential diagnosis of a verrucous squamous cell carcinoma may need to be excluded histologically. Squamous cell papillomas have been related to human papilloma virus infection.

**Granular cell tumours** of the gastrointestinal tract represent 5% of all granular cell tumours in the human body, 25% of which are located in the oesophagus. Nearly two-thirds of these tumours have been found in the lower third of the oesophagus, where they arise in the submucosa as endoscopically pale yellow sessile or polypoid lesions covered by normal mucosa. Histologically, the tumour cells are uniform large, plump cells with eosinophilic granular cytoplasm that are periodic acid-Schiff (PAS) and S100 positive. The covering squamous epithelium is often thickened and can show pseudoepitheliomatous hyperplasia, which may be misdiagnosed as squamous cell carcinoma if only superficial biopsies are taken.

**Malignant tumours of the oesophagus and the gastro-oesophageal junction**

**Squamous cell carcinoma**

**Precursor lesions of squamous cell carcinoma**

Oesophageal squamous cell carcinoma development is believed to be a multistep process from normal squamous epithelium via intraepithelial neoplasia (synonym: dysplasia) to invasive carcinoma based on findings in high-risk populations where dysplasia predate the development of carcinoma by approximately 5 years.\(^1,2\) Dysplasia is defined as the presence of unequivocal neoplastic cells within the epithelium. Squamous cell dysplasia is classified as ‘low-grade’ when architectural and cytological abnormalities are seen in the basal half of the squamous epithelium with preserved maturation of the upper half and as ‘high-grade’ when more than the bottom half shows architectural and cytological abnormalities. Full-thickness dysplasia of the squamous epithelium is referred to as ‘carcinoma in situ’ or ‘non-invasive carcinoma’ by some authors. However, the use of the term ‘carcinoma in situ’ or ‘non-invasive carcinoma’ is strongly discouraged in the clinical routine to ensure clear separation of high-grade dysplasia from invasive carcinoma for patient management.

**Squamous cell carcinoma** is per definition a neoplasm that at least penetrates the epithelial basement membrane into the lamina propria. It is the most common malignant epithelial tumour of the oesophagus worldwide and affects males two to ten times more often than females, with an average age between 50 and 60 years at time of diagnosis. There is a marked geographic and ethnic variation in incidence. Incidence rates are highest in Iran, China, South America and Eastern Africa and are higher in African-Americans than Caucasian-Americans.

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| The aetiology and predisposing factors for oesophageal squamous cell carcinoma vary significantly among different regions in the world.\(^3\) Tobacco-smoking, alcohol and hot beverages such as hot mate tea are major risk factors for oesophageal squamous cell carcinoma.\(^4,5\) |

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Dietary factors such as low intake of fresh fruits and vegetables and high intake of barbecued meat or pickled vegetables most likely play a role in the aetiology of squamous cell carcinoma. The role of human papilloma virus (HPV) infection in the pathogenesis of oesophageal squamous cell carcinoma is still controversial at this moment in time. Patients with achalasia have an increased risk of developing squamous cell cancer\(^6\) as do patients with coeliac disease,\(^7\) Plummer–Vinson syndrome (also called Paterson–Kelly syndrome),\(^8\) tylosis (also called focal non-epidermolytic palmoplantar keratodema),\(^9,10\) previous ingestion of corrosive substances,\(^11\) Zenker’s diverticulum\(^12\) or after ionising radiation.\(^13\) In the Asian population, polymorphisms in *ALDH1B1* and *ALDH2*, both genes encoding aldehyde dehydrogenases, are associated with squamous cell carcinoma.\(^14\)

Oesophageal squamous cell carcinomas are found in the upper, middle and lower third of the oesophagus in a ratio of approximately 1:5:2. The native (untreated) macroscopic appearance of the tumour depends on the depth of tumour invasion and is classified into four different types according to the Japanese Esophageal Society\(^15\) which is similar to the macroscopic classification of gastric cancer (Fig. 1.1). Approximately 60% of squamous cell carcinomas show an exophytic or fungating growth pattern (Fig. 1.2), 25% are ulcerative and 15% are infiltrative.

Squamous cell carcinomas can grow horizontally and vertically. In the West, 60% of patients have carcinomas that have invaded beyond the muscularis propria and have regional lymph node metastases at the time of diagnosis. In contrast, in Japan, up to 40% of all
Figure 1.1 • (a) Borrmann classification for advanced oesophageal and gastric cancers. Type I: polypoid with a broad base, may be superficially ulcerated. Type II: excavated ulcerated lesion with elevated borders, sharp margin with no definitive infiltration into adjacent mucosa. Type III: ulcerative, diffusely infiltrating base. Type IV: diffusely infiltrative thickening of the wall (linitis plastica). (b) Murakami classification for early cancers. Modified from Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 3rd English edition. Gastric Cancer 2011;14(2):101–12.

Figure 1.2 • Oesophageal squamous cell carcinoma located in the middle oesophagus. (a) Fresh oesophagectomy specimen with a polypoid exophytic tumour growth and a smaller flat (red-coloured) mucosal abnormality. (b) Lack of (dark) iodine staining in the abnormal areas. (c) Same specimen after fixation. Courtesy of Dr Tomio Arai, Tokyo, Japan.
Resected oesophageal carcinomas are superficial or early carcinomas involving mucosa and submucosa only. The frequency of lymph node metastases is related to the depth of tumour invasion in the wall (5% for intramucosal carcinomas, about 45% for submucosal carcinomas). Although tumours located in the upper third of the oesophagus are more likely to spread to cervical and upper mediastinal nodes, a significant proportion will also spread to perigastric nodes.

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**Figure 1.3** • Histological images of squamous cell carcinoma. (a) Moderate to well-differentiated squamous cell carcinoma showing evidence of keratinisation (* indicates area with keratinisation). (b) Poorly differentiated squamous cell carcinoma with small islands and strands of tumour cells within desmoplastic stroma without evidence of keratinisation.
Molecular pathology of squamous cell carcinoma

It can be difficult to distinguish between poorly differentiated squamous cell carcinomas and poorly differentiated adenocarcinoma based on the haematoxylin/eosin stained section. In this context, an immunohistochemical marker panel is used in clinical routine to establish the diagnosis. Squamous cell cancers are usually immunopositive for CK5/6, CK14, p63, as well as p40 and negative for CK7, CK20 and CDX2.

To date, there are no molecular markers usable in clinical routine practice in patients with squamous cell carcinoma to predict prognosis or response to chemotherapy.

In the research setting, a number of genomic changes have been described, initially by evaluating single genes. Mutation with consecutive loss or inactivation of the tumour suppressor gene p53 has been found in up to 80% of squamous cell carcinomas. Furthermore, mutations are seen frequently in the RB (retinoblastoma) gene as well as in p16. Amplification (e.g. an increase in the gene copy number) and subsequent protein overexpression of cyclin D1, a cell cycle regulating gene, occurs in 20–40% of squamous cell carcinomas. Inactivation of Fhit (fragile histidine triad gene, a presumed tumour suppressor gene on chromosome 3p14), DLEC1 (deleted in lung and oesophageal cancer-1) and DECI (deleted in oesophageal cancer-1) by genetic or epigenetic mechanisms has recently been shown. Amplifications of proto-oncogenes and growth factors such as FGFR4 and FGFR6 (fibroblast growth factor 4 and 6), EGFR (epidermal growth factor receptor) and MYC have also been described in oesophageal squamous cell carcinoma. More recent studies using next generation sequencing technology have comprehensively characterised oesophageal squamous cancers and identified particular mutations, copy number alterations and genomic rearrangements, significantly increasing our understanding of the genomic landscape of squamous cell carcinoma. After appropriate prospective validation it is expected that the molecular classification may enable personalisation of therapy in the future.

Adenocarcinoma

Precursor lesion of adenocarcinoma

The normal oesophagus is lined with squamous epithelium with a sharp transition to gastric cardia-type mucosa at the Z line. Columnar epithelium in the oesophagus in combination with ulceration and oesophagitis was first described in 1950 by Norman Barrett, who was convinced that this was due to a congenitally short oesophagus. Moersch et al. and Hayward were the first to suggest that the columnar lining of the oesophagus might be an acquired condition due to gastro-oesophageal reflux. Experiments conducted by Bremner et al. in 1970 in a dog model of gastro-oesophageal reflux strongly supported this concept. For a histological illustration of Barrett’s oesophagus, see Fig. 1.5.

Barrett’s oesophagus is defined as an oesophagus in which any portion of the normal distal squamous lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically above the gastro-oesophageal junction and confirmed histopathologically. In the UK, presence of intestinal metaplasia is considered highly corroborative but not specific for a diagnosis of Barrett’s oesophagus.
The risk of developing adenocarcinoma appears to be related to the length of the metaplastic mucosa, with 3 cm being used as the cut-off between a ‘short’ and a ‘long’ segment Barrett’s oesophagus. The relative risk of developing adenocarcinoma in patients with Barrett’s oesophagus is increased, but interestingly, only 5% of patients with oesophageal adenocarcinoma have had a previous diagnosis of Barrett’s oesophagus.

Further details about Barrett’s oesophagus, including the proposed metaplasia–dysplasia–adenocarcinoma sequence and molecular pathology findings, can be found in Chapter 15. Other risk factors of oesophageal adenocarcinoma are tobacco smoking, obesity, which promotes gastro-oesophageal reflux, and use of medications that lower stomach acidity or relax the gastro-oesophageal sphincter. No clear association has been found between alcohol consumption or diet and adenocarcinoma. Case-control studies seem to indicate that infection with *Helicobacter pylori* is protective against oesophageal adenocarcinoma.

Adenocarcinoma is histologically defined as a malignant epithelial tumour with glandular differentiation that has at least infiltrated into the lamina propria. Population-based studies in the USA and Europe indicate that the incidence of oesophageal adenocarcinoma, adenocarcinoma of the gastro-oesophageal junction and proximal stomach has doubled between the 1970s and late 1980s, and continues to increase by 5% every year. Countries with the highest incidence of oesophageal adenocarcinoma are the UK, Australia, the Netherlands and the USA. Oesophageal adenocarcinoma is much more common in males (male: female ratio 4:1 to 7:1) and 80% of oesophageal adenocarcinomas occur in the white population.

Barrett’s oesophagus-associated adenocarcinomas are located almost exclusively in the distal third of the oesophagus and often infiltrate into the proximal stomach (Fig. 1.6). The macroscopic

*Figure 1.5* • Histology of Barrett’s oesophagus. Haematoxylin/eosin-stained slide showing normal squamous epithelium on the left (*) and directly adjacent intestinal-type mucosa with goblet cells as can be seen in Barrett’s oesophagus. No evidence of dysplasia.

Ninety-five per cent of oesophageal adenocarcinomas are associated with Barrett’s oesophagus, which has been identified as the single most important risk factor.

*Figure 1.6* • Macroscopy of a distal oesophagectomy with Barrett’s oesophagus and adenocarcinoma. An irregular, partly ulcerated tumour (black circle) is located at the gastro-oesophageal junction. Between the proximal edge of the tumour and the squamous lined oesophagus is metaplasic columnar epithelium. The squamocolumnar junction (border between the pale-appearing squamous epithelium and brownish-appearing metaplasic epithelium) is located at least 2.5 cm proximal to the gastro-oesophageal junction. Courtesy of Dr B. Disep, Newcastle, UK.
appearances of a locally advanced adenocarcinoma are similar to that of squamous cell carcinoma or gastric adenocarcinoma (see Fig. 1.1). Histologically, oesophageal adenocarcinoma are papillary and/or tubular (intestinal-type according to Laurén classification) and are graded as well, moderately or poorly differentiated according to the proportion of tumour that is composed of glands (see also gastric adenocarcinoma). Approximately 10% of all oesophageal adenocarcinomas are of mucinous or signet ring cell-type. Most patients present with locally advanced disease, e.g. tumour extension into the peri-oesophageal fat and involvement of regional lymph nodes. Should the patient present with early disease, it is important to remember there is a double muscularis mucosae in many cases with Barrett’s oesophagus. Carcinomas infiltrating between the two layers of the muscularis mucosae are still classified as intramucosal (pT1a) cancers. However, carcinomas that have infiltrated into the double muscularis mucosae have been associated with a higher frequency of lymphoangiinvasion and lymph node metastases.

There is an ongoing debate whether adenocarcinoma in the proximity of the oesophagogastric junction should be classified as oesophageal or gastric carcinoma, as both entities are treated with different multimodal therapy approaches. One problem is the lack of worldwide consensus on the definition of the ‘gastro-oesophageal junction’ (see WHO classification of digestive cancer, 4e, 2010). The British Society of Gastroenterology guideline on the diagnosis and management of Barrett’s oesophagus recommends using the distal end of the palisade vessels or the proximal end of the gastric folds to delineate the gastro-oesophageal junction. Siewert et al. defined different types of adenocarcinoma of the gastro-oesophageal junction based on the location of the ‘tumour epicentre’ by combining clinical preoperative findings (radiology, endoscopy) with intra-/postoperative observations:

- **Type I**: Adenocarcinoma of the distal oesophagus, which may infiltrate the gastro-oesophageal junction from above. This entity is also referred to as ‘Barrett carcinoma’. These adenocarcinomas have their centre within 1 cm to 5 cm above the anatomic gastro-oesophageal junction.

- **Type II**: ‘True carcinoma of the cardia’ arising from gastric cardia epithelium or from short segments of metaplastic columnar epithelium at the gastro-oesophageal junction. This entity is also referred to as ‘junctional carcinoma’. These adenocarcinomas have their centre within 1 cm above and 2 cm below the anatomic gastro-oesophageal junction.

- **Type III**: Subcardial gastric carcinoma, which infiltrates the oesophagogastric junction and distal oesophagus from below. This entity is also referred to as ‘proximal gastric carcinoma’. These adenocarcinomas have their centre within 2 cm and 5 cm below the anatomic gastro-oesophageal junction.

**Variants of oesophageal adenocarcinoma**

1. **Truly non-Barrett’s oesophagus-associated adenocarcinoma** is rare and may arise either from heterotopic gastric mucosa (so called ‘gastric inlet’), which can be anywhere in the oesophagus, or from the epithelium of submucosal oesophageal glands.

2. **Adenoid cystic carcinoma** is very rare. These carcinomas are histologically identical to salivary gland-type adenoid cystic carcinoma and occur more frequently in females. They are thought to arise from submucosal oesophageal glands and usually form well-circumscribed solid nodules in the submucosa with the overlying squamous epithelium showing no abnormality. Most tumours show some differentiation towards squamous, glandular or even small-cell elements which would indicate an origin from a multipotential stem cell.

Details about dysplasia as a precursor lesion of oesophageal adenocarcinoma and molecular pathology of oesophageal adenocarcinoma are provided in Chapter 15.

**Neuroendocrine tumours**

Neuroendocrine tumours (NET), neuroendocrine carcinomas (NEC) and mixed adenoneuroendocrine carcinomas (MANECs) of the oesophagus are classified in the same way as those in the rest of the gastrointestinal tract using immunohistochemistry for synaptophysin and chromogranin A, both markers for neuroendocrine differentiation, and Ki67 (proliferation index required for grading). Oesophageal neuroendocrine tumours are exceedingly rare and mostly located in the distal oesophagus. The majority are poorly differentiated neuroendocrine (small cell) carcinomas, which are highly aggressive with a median survival of 6–12 months or less. Histologically, these may appear as homogeneous tumours (Fig. 1.7) or consist of a mixture of squamous and mucopidermoid elements. As histological features including immunohistochemical markers are similar to small cell carcinoma of the lung, the possibility of metastatic or direct spread from the lung should always be considered in the differential diagnosis.
Stomach

Benign tumours and tumour-like lesions of the stomach

Gastric polyps

Gastric polyps are usually found incidentally during endoscopy. According to the cell of origin, polyps can be epithelial (fundic gland polyp, hyperplastic polyp, adenomatous polyp), neuroendocrine, lymphohistiocytic (xanthelasma, lymphoid hyperplasia), mesenchymal (gastrointestinal stromal tumour, neural or vascular tumours) or mixed. They can be sporadic or occur as part of a syndrome.

Fundic gland polyps are the most common type of gastric polyps and were originally described in patients with familial adenomatous polyposis (FAP) syndrome. Sporadic fundic gland polyps are found in up to 11% of patients, are more common in middle-aged women and are typically single or few in number, measuring less than 0.5 cm. The incidence of fundic gland polyps is low in patients with H. pylori infection and relatively high in patients taking proton pump inhibitors. While low-grade dysplasia is frequent in FAP patients with fundic gland polyps, dysplasia is rare in sporadic cases. Other lesions that can endoscopically appear as polyps in the stomach are: inflammatory fibroid polyps which consist of benign submucosal proliferations of spindle cells, small vessels and inflammatory cells; xanthomas, which consist of aggregates of lipid-laden macrophages embedded in the lamina propria; lipomas, which are circumscribed masses of adipose tissue without atypia usually located in the submucosa and pancreatic heterotopias.

Adenomatous polyps are subdivided into classic intestinal-type adenomas and non-intestinal-type adenomas. The latter are less common and characterised by gastric-type differentiation. Non-intestinal-type gastric adenoma such as pyloric gland adenoma, foveolar adenoma and chief cell adenoma are very rare and not further discussed here.

Sporadic intestinal-type adenomas are most common in patients over 50 years of age, three times more frequent in men and most frequently found at the lesser curve of the antrum. They are usually solitary, less than 2 cm in diameter, well circumscribed, pedunculated or sessile and their prevalence varies widely from 4% in Western countries to 27% in Japan. Adenomatous polyps are precursors of gastric adenocarcinomas and the risk of adenocarcinoma seems to increase with increasing size. Fifty per cent of adenomatous polyps >2 cm harbour an adenocarcinoma.

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Polyposis syndromes

Hamartomatous polyps in the stomach have been found in patients with Peutz–Jeghers syndrome, juvenile polyposis, Cronkhite–Canada syndrome and Cowden disease. With the exception of Peutz–Jeghers polyps, the histological features of these polyps overlap with those of sporadic hyperplastic polyps. The pathological diagnosis of a ‘syndromic polyp’ requires knowledge of the clinical context. All patients with above-mentioned polyposis syndromes have an increased risk of developing gastric carcinoma, which appears to be highest in patients with Peutz–Jeghers syndrome, at 30%. Up to 80% of patients with Peutz–Jeghers syndrome

Figure 1.7 • Microscopic image of a neuroendocrine carcinoma.

Seventy-five per cent of FAP-associated fundic gland polyps show an APC mutation, whereas sporadic fundic gland polyps are devoid of APC mutations and harbour CTNNB1 (β-catenin) mutations in up to 90%.

Fundic gland polyps have been considered as being hamartomatous lesions in the past, a view that has been challenged recently. Hyperplastic polyps are composed of epithelial and stromal components and are most frequently found in the antrum of patients with inflamed or atrophic gastric mucosa. A recent review of more than 8000 gastric polyps showed that 14% were hyperplastic polyps. Hyperplastic gastric polyps are thought to arise as a hyperproliferative response of the gastric foveoleae to tissue injury. Removal of the underlying injury such as H. pylori infection resulted in regression of the hyperplastic polyps in 70% of patients. Up to 20% of hyperplastic polyps show foci of dysplasia, p53 mutations, chromosomal aberrations and microsatellite instability which seem to be related to larger size (>2 cm). Hyperplastic polyps should be regarded as surrogate markers of cancer risk and synchronous or metachronous gastric carcinomas have been reported in up to 6% of cases.

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have a germline mutation of the STK11/LKB1 gene, which encodes an enzyme responsible for cell division, differentiation and signal transduction. The most common genetic alterations in patients with juvenile polyposis are germline mutation of SMAD4 or BMPRIA, both genes implicated in the TGFbeta signalling pathway. Cowden disease is caused by germline mutations of PTEN, resulting in multiple hamartomas involving multiple different organs. Cronkhite–Canada syndrome is a non-inherited polyposis syndrome of unknown pathogenesis.

**Gastric carcinoma**

**Epidemiology**

Despite a steady decline of gastric carcinoma incidence at a rate of approximately 5% per year since the 1950s, gastric carcinoma is still the fifth most common carcinoma in the world, with nearly one million people newly diagnosed per year, representing 8% of all new cancers diagnosed per year in the world. Age-standardised incidence rates of gastric carcinoma are twice as high in males as in females and show prominent geographical variation, ranging from 3.9 per 100,000 males in Northern Africa to 42.4 in Eastern Asia. Approximately 75% of all gastric carcinoma are diagnosed in Asia. Gastric carcinoma is the third leading cause of cancer death in both sexes worldwide, responsible for 10% of all cancer deaths. A male: female ratio of 2:1 has been reported for non-cardia gastric carcinoma in contrast to a male: female ratio of 5:1 for gastric cardia carcinoma.

**Aetiology and risk factors**

Ten per cent of gastric carcinomas show familial clustering, but only 1–3% of gastric carcinomas are related to identified inherited gastric carcinoma predisposition syndromes such as hereditary diffuse gastric carcinoma (HDGC), hereditary non-polyposis colon cancer (Lynch syndrome), familial adenomatous polyposis (FAP), Peutz–Jeghers syndrome, Li–Fraumeni syndrome and familial breast and ovarian cancer. One of the defining characteristics of HDGC is the presence of a germline CDH1 (Ecadherin) mutation. The lifetime risk of developing gastric carcinoma in CDH1 mutation carriers is 67% in males and 83% in females. HDGC will be covered in greater detail in Chapter 2.

*Helicobacter pylori* infection increases the risk of gastric carcinoma up to sixfold and represents one of the most important environmental risk factors for the development of gastric carcinoma. Humans are the only known host for *H. pylori*, which can colonise the gastric body and the antrum (Fig. 1.8). The development of gastric carcinoma after *H. pylori* infection has been considered as a multistep process progressing from chronic active pan- or corpus-predominant gastritis to increasing loss of gastric glands (atrophy), replacement of the normal mucosa by intestinal metaplasia and malignant transformation.

However, most *H. pylori*-infected individuals will remain asymptomatic and only 1–5% of the infected population will develop gastric carcinoma, a phenomenon that has been attributed to different bacterial strains, host-inflammatory genetic susceptibility and in particular *H. pylori* virulence factors vacuolating cytotoxin antigen (VacA) and cytotoxin-associated gene A antigen (CagA).

It has been estimated that 10% of gastric carcinomas are associated with Epstein–Barr virus (EBV) infection. In contrast to *H. pylori*, which has a role in the early stage of gastric carcinoma development as it can only bind to the surface of the normal gastric epithelial cell but not to the surface of gastric carcinoma cells, EBV is absent in normal or dysplastic gastric epithelial cells but present in gastric carcinoma cells. For unknown reasons, EBV prevalence is higher in gastric stump cancer.

The prominent geographic variation in gastric carcinoma incidence suggests that other environmental factors, such as diet, might play an important aetiological role. However, evidence for fruit and vegetable consumption, vitamin C supplementation, dietary salt and nitroso compounds, is still conflicting.

A dose-dependent relationship between smoking and gastric carcinoma risk has been shown in prospective studies and it has been estimated that 18% of gastric carcinomas in the European population were attributable to smoking. There is currently no conclusive evidence for an association between alcohol consumption and gastric carcinoma. An increased risk of gastric carcinoma after previous gastric surgery for benign peptic ulcer disease has been reported.

**Lesions predisposing to gastric carcinoma**

The natural history of sporadic gastric carcinoma development is thought to be a multistep process. Correa postulated a sequence from chronic atrophic gastritis, intestinal metaplasia, dysplasia and gastric carcinoma based on histopathological findings.

Ten years later and again more recently, this model was expanded by Yasui et al. to include stepwise molecular alterations. This subject is covered in more detail in Chapter 2.
Chronic atrophic gastritis and intestinal metaplasia

Inflammation of the gastric mucosa is most commonly the result of bacterial infection (most commonly due to *H. pylori* infection), chemical agents (non-steroidal anti-inflammatory drugs (NSAIDS), alcohol, bile reflux) or the consequence of an autoimmune process (i.e. autoimmune gastritis due to parietal cell auto-antibodies). Chronic inflammation can either result in the shrinkage or complete disappearance of the typical gastric glands followed by replacement fibrosis of the lamina propria or the replacement of the native glands by metaplastic glands (i.e. intestinal and/or pseudopyloric metaplasia). Under both conditions, there is ‘atrophy’ (loss of native gastric glands), but only the presence of metaplastic glands is considered a condition with an increased risk of carcinoma development (Fig. 1.9).

Two main types of intestinal metaplasia have been identified depending on whether the epithelium is similar to small bowel epithelium or large bowel epithelium and on the histochemical characteristics of the mucin. Type I = complete, small bowel type, positive for neutral mucin and sialomucin, negative for sulfomucin; type II/III = incomplete, large bowel type, positive or negative for neutral mucin, positive for sialomucin and sulfomucin (Fig. 1.10).

Chronic gastric ulcer

Chronic gastric ulcers are typically located at the edge of atrophic mucosa. If a chronic gastric ulcer is detected on endoscopy, it should be considered malignant until histology has proven otherwise. Patients with gastric

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**Figure 1.8** Special staining procedures to detect *Helicobacter pylori* in gastric biopsies. (a) Immunohistochemical staining demonstrates the organisms as brown rods in the epithelial surface. (b) Warthin-Starry silver staining shows individual spiral-shaped (black-coloured) organisms densely populating the surface epithelium.

**Figure 1.9** Microscopic image showing gastric atrophy.

- Some but not all studies indicate that there is a positive correlation between cancer risk and degree and extent of incomplete intestinal metaplasia.  

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Pathology of oesophageal and gastric tumours

Ulcer have an increased risk for gastric carcinoma as gastric ulcer and gastric carcinoma have the same risk factors. Five per cent of endoscopically benign ulcers eventually prove to be malignant. However, overall, less than 1% of all gastric carcinomas develop in pre-existing peptic ulcers.

Gastric polyps
These are discussed above.

Gastric dysplasia
Gastric dysplasia (synonym: intraepithelial neoplasia) can have a flat, slightly depressed or polypoid growth pattern. In Europe and North America polypoid dysplasia is termed ‘adenoma’ whereas in Japan, dysplasia with any growth pattern is called ‘adenoma’.

The prevalence of gastric dysplasia varies between 20% in high-risk areas in Asia and 4% in Western countries. Dysplasia is more frequent in males, patients over the age of 70 years and most commonly affects the lesser curve and the antrum. Histologically, dysplasia is characterised by architectural as well as cytological atypia and is stratified into two grades, low- and high-grade. Low-grade dysplasia progresses to adenocarcinoma in up to 23% of cases within 10 months to 4 years, whereas malignant transformation of high-grade dysplasia has been reported to occur in 60–80% of cases.

Whilst chromosomal and microsatellite instability, APC and p53 mutations, as well as CpG-island methylation, have all been found in gastric dysplasia, none of these molecular findings is specific enough to establish and support the diagnosis of dysplasia in routine clinical practice.

Early and advanced gastric carcinoma
Early gastric carcinoma is defined as adenocarcinoma limited to the mucosa or submucosa with or without regional lymph node metastases. The term ‘early’ does not refer to the size or age of the lesion. Gastric carcinoma infiltrating into the muscularis propria and beyond is defined as ‘advanced’. These two categories of gastric carcinoma differ not only in prognosis but also often with respect to morphology and clinical aspects. Early gastric carcinoma has an excellent prognosis, with a 5-year survival rate exceeding 90% in Japan. The 5-year survival rate of advanced gastric carcinomas, the most frequent type in the West, is around 23% when treated by surgery alone and around 36% when treatment includes perioperative cytotoxic chemotherapy.

Long-term follow-up studies have shown that the tumour growth rate can differ significantly between early and advanced carcinomas; a doubling time of several years for early carcinoma but less than a year for advanced carcinoma has been estimated. The macroscopic appearance differs between early and advanced gastric carcinoma.

The macroscopic growth pattern of advanced carcinomas is classified according to Borrmann into four major types. Type 5 is used for unclassifiable cancers. Early gastric carcinomas are macroscopically Borrmann type ‘0’ and classified according to Murakami as protruding, superficial elevated/flat/depressed and excavated (Figs 1.1 and 1.11).

The classification of the macroscopic tumour appearance can be used by radiologists, endoscopists and pathologists alike. Consistent use of this macroscopic classification can greatly improve the communication

Figure 1.10 • Incomplete intestinal metaplasia (type III) with siaIomucins (blue-greenish) in goblet cells and neutral and sulfomucins (dark brown) in columnar cells. (Alcian blue-high-iron diamine staining technique to differentiate different mucin types).

Box 1.1 • Vienna classification of epithelial neoplasms of the gastrointestinal tract

1. Negative for neoplasia
2. Indefinite for neoplasia
3. Non-invasive low-grade neoplasia
4. Non-invasive high-grade neoplasia:
   4.1 High-grade adenoma
   4.2 Non-invasive carcinoma
   4.3 Suspicious for invasive carcinoma
5. Invasive adenocarcinoma:
   5.1 Intramucosal carcinoma
   5.2 Submucosal carcinoma or beyond
within the multidisciplinary treatment team. Interestingly, approximately 10% of gastric carcinomas retain their endoscopic and radiologic ‘early cancer’ appearance as they progress to advanced stage. This may lead to a potential underestimation of the ‘true’ clinical disease stage at the time of diagnosis.

In Japan, approximately 2% of early gastric carcinoma recur after curative resection. Submucosal invasion, lymph node metastases and differentiated type histology have been associated with increased risk of recurrence. Differentiated histology is a risk factor for recurrence as cancers with differentiated histology show a higher incidence of haematogenous spread compared to undifferentiated cancers which are more prone to recur in lymph nodes or serosa-lined cavities. The incidence of lymph node metastases is 2–3% for intramucosal carcinomas and 20–30% for submucosal carcinomas.

For advanced gastric carcinoma, depth of infiltration into the wall (T stage) and number of lymph nodes with metastatic tumour (N stage) remain the strongest prognostic indicators.

Morphological subtypes of gastric carcinoma

The histology of gastric carcinoma is characterised by marked intra- and inter-tumoural heterogeneity. The variability of the histological appearance seems to increase with increasing depth of infiltration into the wall and increasing age at time of diagnosis. As a result of this marked morphological diversity, a number of different classification systems have been advocated by different authors such as Laurén, Ming, Nakamura, Mulligan, Goseki, Carneiro and the World Health Organisation (WHO). The histological classification according to Laurén (intestinal-type versus diffuse-type versus mixed-type), Ming (expanding-type versus infiltrative-type) and WHO (tubular versus papillary versus mucinous versus poorly cohesive including signet ring versus mixed) are the classifications most commonly used outside of Japan.
In Japan, the recommended histological typing is similar but not 100% identical to the WHO classification. In the West, 60–70% of gastric carcinomas are classified as intestinal-type according to Laurén (Fig. 1.12a). Intestinal-type carcinomas are usually sharply demarcated and have a pushing margin according to Ming’s classification. Laurén’s diffuse-type is composed of scattered poorly cohesive cells or small clusters of cells and is diffusely infiltrative (Fig. 1.12b). Cells may contain cytoplasmic mucus, which compresses the nucleus to sickle-like shape and gives the whole cell a ‘signet ring’ cell appearance (Fig. 1.12c). Gastric carcinomas that consist of approximately 50% diffuse and 50% intestinal type, solid type carcinomas and others that cannot be classified as diffuse or intestinal are called indeterminate, unclassifiable or mixed. Intestinal-type carcinomas are more common in men over 60 years of age, in high-risk countries, are located in the antrum, show a Borrmann type II growth pattern and metastasise to the liver. In contrast, diffuse-type carcinomas are more common in younger females, have a similar incidence in most countries, are located predominantly in the proximal body of the stomach and show a linitis plastic-type growth pattern with transperitoneal metastases.

Gastric carcinomas are graded as well differentiated (more than 90% of the carcinoma consists of well-formed glands), moderately differentiated (intermediate between well and poor) and poorly differentiated (highly irregular glands which may be difficult to be recognised as glands). Grading of tumour differentiation is prone to considerable inter-observer variation and the value of the histological subtyping and/or tumour grading in predicting patient prognosis is still controversial.

Rare morphological variants of gastric carcinoma
Gastric carcinomas with prominent lymphoid stroma (so called medullary carcinoma) are associated with EBV infection in 80% of cases. Medullary carcinomas are predominantly located in the proximal stomach and are more common in the remnant stomach. The prognosis of this subtype is better than conventional gastric carcinoma, with a 5-year survival rate of 75%.

Figure 1.12 • (a) Intestinal-type carcinoma tubular subtype composed of irregularly sized and shaped glandular structures with mildly pleomorphic nuclei. However, this tumour is admixed with poorly differentiated tubular structures with large cells and bizarre-shaped nuclei. (b) Diffuse-type carcinoma. Poorly cohesive single cells are diffusely infiltrating the smooth muscle wall. (c) Signet ring cell carcinoma. The neoplastic cells are characterised by large amounts of intracytoplasmic mucin (almost ‘clear’ cytoplasm) with eccentrically located and mostly flattened nuclei.
Hepatoid and alpha-fetoprotein-producing carcinomas are particular aggressive carcinomas with high AFP serum levels. Adenosquamous carcinomas consist of at least 25% squamous elements. These tumours are deeply invasive and associated with lymphovascular invasion and poor prognosis.

Molecular pathology of gastric carcinoma

Adenocarcinomas of the stomach are immunohistochemically identified in the clinical histopathology routine setting by using a panel of markers. Gastric cancers are usually positive for CK7, CDX2 (usually only intestinal-type cancers) and negative for CK20, CK5/6, CK14, p63 and p40.

Since recently, and depending on the clinical context, material from patients with metastatic gastric cancer requires testing for eligibility for treatment with trastuzumab by immunohistochemistry ± in situ hybridisation for HER2 (Fig. 1.13; Box 1.2).

The only two targeted therapies which are currently approved for use in patients with metastatic gastric carcinoma are trastuzumab, which targets the human epidermal growth factor receptor 2 (HER2) and ramucirumab targeting VEGFR. HER2 is more commonly amplified and overexpressed in intestinal-type carcinoma.

Looking at individual genes, the first gene found to be amplified in gastric carcinoma was c-MYC in 1984, and the first oncogene discovered in gastric carcinoma was FGF4 in 1986.

\( c\)-MET is a transmembrane tyrosine kinase receptor and was found to be amplified at higher frequency in diffuse-type gastric carcinoma. Overexpression of \( c\)-MET has been related to tumour stage. Fibroblast growth factor receptor 2 (FGFR2) is another potential drug target and FGFR2 amplification has been detected in gastric carcinoma. Unfortunately, recent trials using c-MET or EGFR or other RTK inhibitors in gastric cancer have not been successful, with the exception of VEGFR inhibitors.

\( p\)-53 mutations have been identified in 60% of gastric carcinoma with approximately equal frequency in different histological subtypes and thus \( p\)-53 is the most frequently mutated gene in gastric carcinoma.

\( APC\) mutations have been observed in 30–40% of well and moderately differentiated intestinal-type gastric carcinoma and in less than 2% of poorly differentiated diffuse-type gastric carcinoma.

Alterations (mutations or gene silencing by methylation) of any of the five human DNA mismatch repair genes, \( MSH2\), \( MLH1\), \( MSH6\), \( PMS1\) and \( PMS2\) result in defective DNA mismatch repair. Tumours with DNA mismatch repair deficiency show variations in the number of short tandem repeat units contained within microsatellites, a phenomenon called microsatellite instability. Cells with defective mismatch repair display substantially elevated numbers of mutations thought to accelerate carcinogenesis and are histologically characterised by a prominent immune cell infiltration, making them candidates for modern immunomodulatory therapy. The reported frequency of microsatellite instability varies between 15% and 38% of gastric carcinoma, is higher in intestinal-type gastric carcinoma and is more common in cancers from older age females and cancers in the antrum.

Yasui et al. considered the above mentioned findings from individual genes and proposed a multistep model of molecular alterations, refining the multistep model of histological changes proposed by Correa. The model by Yasui has been recently updated (see Fig. 1.14), suggesting that there are at least four different molecular pathways to develop differentiated and undifferentiated type of gastric cancer. However, some molecular alterations have been identified in both histological subtypes and therefore may occur during the early stages of cancer development. Whilst the work from Correa and Yasui focuses on the different steps implicated in the development of gastric cancer, a number of recent comprehensive multi-platform genomic studies identified gastric cancer subtypes based on their molecular characteristics (for overview see references 100–102). Some of them offer potential new prognostic and predictive markers. However, all of them require validation in large clinical series to establish their clinical relevance.

Macroscopy and microscopy of epithelial tumours of the oesophagus and stomach after neoadjuvant therapy

The macroscopic appearance of epithelial tumours can change dramatically after preoperative chemo(radio)
### Box 1.2  •  HER2 scoring system for gastric cancer

<table>
<thead>
<tr>
<th>Surgical specimen staining pattern</th>
<th>Biopsy specimen staining pattern</th>
<th>HER2 assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt;10% of tumour cells</td>
<td>No reactivity or no membranous reactivity in any tumour cell</td>
</tr>
<tr>
<td>1+</td>
<td>Faint or barely perceptible membranous reactivity in ≤10% of tumour cells; cells are reactive only in part of their membrane</td>
<td>Tumour cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of tumour cells stained</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≤10% of tumour cells</td>
<td>Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≤10% of tumour cells</td>
<td>Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
</tr>
</tbody>
</table>


**Figure 1.14  •  Clinicopathologic and molecular characteristics of gastric cancer.** Adapted from Cancer Sci 2015;106(8):951–8.
therapy depending on the extent of tumour response. These changes can be asymmetric, thus for the classification of tumours according to the Siewert or TNM classification into oesophageal, junctional or gastric cancer, it is recommended to use the pre-treatment findings.

Histologically, squamous cell carcinoma and adenocarcinoma appearance can change after neoadjuvant chemo(radio)therapy showing extensive necrosis, inflammation, fibrosis and foreign body type granulomas around keratin pearls. The regression grading according to Mandard et al.\textsuperscript{103} considers the relative proportion of residual viable tumour cells and fibrosis in the primary cancer and is currently the one most commonly used in the UK. Very recently, a grading system to assess tumour regression in lymph nodes has been proposed and showed prognostic significance in a small series of patients.\textsuperscript{104} There is also evidence that lymph node status after preoperative chemotherapy is more relevant for predicting prognosis than primary tumour regression.

**Neuroendocrine tumours of the stomach**
The gastric mucosa contains several types of neuroendocrine cells, which produce neurotransmitter, neuromodulator or neuropeptide hormones and releases them into the bloodstream. These cells are usually immunoreactive for chromogranin A and synaptophysin.\textsuperscript{106} Neuroendocrine tumours (previously known as ‘carcinoids’) arise most commonly from enterochromaffin-like (ECL) cells. Hypergastrinaemia due to unregulated hormone release by a gastrinoma or due to hyperplasia of gastrin-producing cells in the antrum secondary to achlorhydria is consistently associated with hyperplasia of the ECL cells.\textsuperscript{107} A multistep progression from simple hyperplasia through nodule formation to dysplasia and tumour formation is thought to occur.

The incidence of gastric neuroendocrine tumours has been increasing over the last decades and accounts for 6% of all gastrointestinal neuroendocrine tumours.\textsuperscript{108} Neuroendocrine tumours of the stomach are almost exclusively located in the body of the stomach.

Three distinct types of neuroendocrine tumours can be distinguished based on their pathogenesis (Table 1.1):\textsuperscript{14}

- **Type 1**: Multiple well-differentiated neuroendocrine tumours affecting predominantly middle-aged females are associated with autoimmune chronic atrophic gastritis and pernicious anaemia due to autoantibodies against parietal cells. This type is the most common type of gastric neuroendocrine tumour. Tumours tend to be limited to the submucosa. Metastases can be found in 7–12% of cases and are usually confined to the local lymph nodes. A reduction in the number of ECL cells can be achieved by treatment with octreotide.\textsuperscript{109}

- **Type 2**: Neuroendocrine tumours associated with the Zollinger–Ellison syndrome (gastrinoma-related syndrome) in patients with multiple endocrine neoplasia (MEN) type 1 have no sex predilection. The tumours tend to be multicentric with minimal gastritis in the background, but both ECL hyperplasia and dysplasia are present. These tumours often extend deep into the muscle wall, have lymph node metastases and have occasionally caused death. The loss of the tumour cell parietal cell autoantibodies against parietal cells.

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>Characteristics of gastric neuroendocrine tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td><strong>Type 2</strong></td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>70–85</td>
</tr>
<tr>
<td>Tumour characteristics</td>
<td>Often small, multiple, polypoid, multicentric</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>63</td>
</tr>
<tr>
<td>Gender</td>
<td>Females &gt; males</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Chronic atrophic gastritis type A</td>
</tr>
<tr>
<td>Serum gastrin levels</td>
<td>Increased</td>
</tr>
<tr>
<td>pH of gastric juice</td>
<td>Increased</td>
</tr>
<tr>
<td>Ki67 (%)</td>
<td>Usually &lt;2</td>
</tr>
<tr>
<td>Metastases (%)</td>
<td>2–5</td>
</tr>
</tbody>
</table>

MEN, multiple endocrine neoplasia; ZES, Zollinger–Ellison syndrome.

suppressor gene MEN1 on chromosome 11q13 is seen in the majority of these tumours, a defect also found in those tumours of the gut, pancreas and parathyroid associated with MEN1.110

• Type 3: Sporadic neuroendocrine tumours which are neither associated with atrophic gastritis nor with MEN1 syndrome. These tumours are usually solitary lesions that occur in middle-aged men. They tend to be larger (>2 cm) and have a more aggressive behaviour. The background mucosa shows no evidence of atrophic gastritis and no evidence of neuroendocrine hyperplasia or dysplasia. Serosal infiltration with lymphatic and vascular invasion and liver metastasis with an accompanying carcinoid syndrome are common. Metastases are present in 52% of cases and approximately one-third of the patients will have died within 51 months.

Grading of neuroendocrine tumours with a combination of the morphological features and the proliferation fraction (mitotic index or Ki67 index) has shown to be of prognostic value.14 Grade 1 neuroendocrine tumours typically have a Ki67 index below 2%, whereas grade 3 tumours are poorly differentiated, have a Ki67 index above 20%, show necrosis and are classified as neuroendocrine carcinomas. Guidelines for the management of gastric neuroendocrine tumours have been updated recently.111

Mesenchymal tumours of the stomach
Non-epithelial tumours such as glomus tumour, inflammatory myofibroblastic tumours, leiomyoma, leiomyosarcoma, schwannoma, synovial sarcoma and Kaposi sarcoma are all relatively rare in the stomach and will not be discussed here.

This chapter will focus on gastrointestinal stromal tumours (GIST), which are the most common primary mesenchymal tumours of the gastrointestinal tract and 60–70% of GISTs occur in the stomach. Most GISTs are sporadic, but they can also be part of syndromes, namely Carney’s triad, Carney Stratakis syndrome, neurofibromatosis type 1 or can be familial due to germline mutations of the c-KIT and PDGFRA genes.

GISTs can occur in any part of the stomach and vary from small nodules in the wall, which are covered by intact mucosa to large masses leading to gastric outlet obstruction. Histologically, most GISTs show a spindle cell morphology with little atypia. Twenty per cent of GISTs show epithelioid histology. GISTs are immunoreactive for c-KIT (CD117), DOG and often also for CD34. Even if all common immunohistochemical markers are unexpectedly negative, it is still legitimate to make the diagnosis of a GIST based on morphology alone. However, those cases should be investigated for relevant mutations. GISTs contain c-KIT or PDGFRA-activating mutations. c-KIT-activating mutations are most frequently found in exon 11 and most GISTs with c-KIT mutations are imatinib-sensitive whereas GISTs with PDGFRA-activating mutations are usually imatinib-resistant. With the exception of very small tumours, all GISTs have the potential to become malignant. The management of gastric GISTs is discussed in detail in Chapter 11.

A combination of site of origin, size and mitotic index has been shown to predict the risk of progressive disease in patients with GISTs (Table 1.2).112

<table>
<thead>
<tr>
<th>Tumour parameters</th>
<th>Risk of progressive disease (metastasis or tumour-related death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic index</td>
<td>Gastric</td>
</tr>
<tr>
<td>≤5 (in 5 mm²)</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>2 to ≤5 cm</td>
<td>Very low (1.9%)</td>
</tr>
<tr>
<td>5 to ≤10 cm</td>
<td>Low (3.6%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>Moderate (10%)</td>
</tr>
<tr>
<td>&gt;5 (in 5 mm²)</td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>None (0%)</td>
</tr>
<tr>
<td>2 to ≤5 cm</td>
<td>Low (4.3%)</td>
</tr>
<tr>
<td>5 to ≤10 cm</td>
<td>High (52%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>High (55%)</td>
</tr>
</tbody>
</table>

Reproduced from Royal College of Pathologists Dataset for gastrointestinal stromal tumours, published February 2012.
Lymphoma of the stomach
Any type of lymphoma can also occur in the gastrointestinal tract, which is the most common extranodal site. Within the gastrointestinal tract, 50–75% of lymphomas are located in the stomach. Some 5–10% of all gastric malignancies are primary lymphomas. The two most common subtypes of primary gastric lymphomas are extranodal marginal-zone lymphoma of the mucosa-associated lymphoid tissue (so called MALT lymphoma) and diffuse large B-cell lymphoma. The incidence of primary gastric lymphoma is similar in men and women.

MALT lymphoma
The majority of MALT lymphomas occur in patients over the age of 50 years, with equal sex distribution, who present clinically with symptoms suggesting a diagnosis of gastritis or peptic ulcer disease. The tumours appear macroscopically as an ill-defined thickening of the mucosa with erosions, sometimes ulcerated (Fig. 1.15) and frequently multifocal. Gastric MALT lymphoma can spread to the regional nodes. MALT lymphoma is composed of neoplastic B-cells, which resemble follicle centre cells and are termed centrocyte-like, whereas other cells show plasma cell differentiation and occasionally there are blast cells. The characteristic lymphoepithelial lesion (Fig. 1.16) is composed of small to medium-sized tumour cells with irregular nuclei that infiltrate the pit epithelium. This lesion is not pathognomonic of a lymphoma as it can also be demonstrated in an H. pylori-associated gastritis, Sjögren’s syndrome and Hashimoto’s thyroiditis.

It is thought that the development of MALT lymphoma is a multistage process initiated by chronic active inflammation due to H. pylori infection. Eradication of H. pylori with antibiotics has been shown to be associated with MALT lymphoma remission in up to 77% of patients within 12 months. Less than 10% relapse, and this could be due to reinfection with H. pylori; in the absence of reinfection, the relapse appears to be self-limiting.

Cytogenetic studies show that three major translocations are seen in MALT lymphomas: t(11:18)(q21;q21)/API2-MALT1 (30–40% of cases), t(14:18)(q32:q21)/IGH-MALT1 and t(1:14)(p22;q32)/IGH-BCL10. Some of the translocations have been related with unresponsiveness to H. pylori eradication. Other translocations are associated with the juxtaposition of BCL10 to the immunoglobulin heavy chain gene resulting in deregulation of the immunoglobulin. In addition, there is loss or mutation of p53, c-MYC mutation, inactivation of p15/p16 by hypermethylation and FAS gene mutation.

Most low-grade MALT lymphomas are associated with disease confined to the gastric mucosa with slow dissemination. The favourable clinical behaviour may reflect the partial dependence on the H. pylori antigenic drive. The progression to the more common high-grade MALT lymphoma is thought to require the acquisition of further genetic abnormalities. Gastric MALT lymphoma with the t(11:18)(q21;q21) translocation should be treated with chemotherapy or radiation together with H. pylori eradication, as H. pylori eradication alone is ineffective. The other lymphomas which are resistant to H. pylori eradication are those with abnormalities of the BCL10 locus or those associated with autoimmune gastritis. These can be identified by strong nuclear staining with anti-BCL10 in the former and in the latter by staining with the product of the FAS oncogene. These non-responsive lymphomas can be treated surgically or by surgery in combination with chemoradiotherapy. The 5-year survival for localised cases is 90–100%. Continued follow-up of these patients is recommended as it is now recognised that synchronous and metachronous adenocarcinomas can occur.

Diffuse large B-cell lymphoma
Primary gastric diffuse large B-cell lymphoma is composed of B-cells with a nuclear size equivalent

Figure 1.15 • Macroscopic image of stomach with lymphoma.

Figure 1.16 • Microscopic image of lymphoepithelial lesion (white arrow).
to a macrophage nucleus or at least twice the size of a normal lymphocyte. Similar to MALT lymphoma, the neoplastic cells destroy the gastric glandular architecture. Up to 50% of diffuse large B-cell lymphomas have foci of MALT lymphomas and regression of diffuse large B-cell lymphoma after eradication of *H. pylori* has been reported. Macroscopically, this lymphoma appears as a large ulcerated mass mimicking advanced gastric carcinoma. Chromosomal translocations involving the immunoglobulin heavy chain gene locus are frequent in diffuse large cell lymphomas resulting in deregulation of *BCL6, BCL2* and *MYC*. In the presence of EBV, diffuse large B-cell lymphomas are more likely to be resistant to chemoradiotherapy.

### Key points

- **The multistep progression from normal mucosa to cancer shows that the p53 gene has been found to be abnormal in up to half the cases of oesophageal squamous cell carcinoma as well as gastric carcinoma. A different type of p53 mutation is found in adenocarcinoma of the oesophagus.** p53 mutations allow cells to proliferate despite having damaged DNA-promoting malignant transformation.

- **Squamous cell dysplasia is regarded as a precancerous condition of the oesophagus.** In screened high-risk populations, the finding of dysplasia predates the development of carcinoma by approximately 5 years.

- **It is difficult to distinguish between distal oesophageal adenocarcinoma and proximal gastric cancer in advanced cancers based on the location of the tumour with respect to the gastro-oesophageal junction.** Intestinal metaplasia can indicate the presence of Barrett’s oesophagus, but can also occur in the stomach.

- **The pathogenesis of gastric carcinoma is complex and multifactorial with several potential precursor lesions including gastric dysplasia.**

- Although it is possible to reverse the inflammatory and some of the intestinal metaplastic changes associated with *H. pylori* infection, atrophy and the colonic-type intestinal metaplasia (type III – incomplete metaplasia) are regarded as irreversible. There is continuing controversy as to the value of identifying the colonic-type mucin and its predictive value in identifying patients at risk of developing cancer.

- **There are several problems associated with histological interpretation of grades of glandular oesophageal and gastric dysplasia; these include high inter-observer variation, distinguishing regenerative atypia from true dysplasia, the ability to differentiate high-grade dysplasia from intramucosal carcinoma, and a lack of experience due to the relative rarity of dysplasia, especially in low incidence Western countries.**

- **There are several classifications for gastric adenocarcinoma, the most widely used being Laurén’s classification.** The tumours are divided into two main types: those that form glandular structures are known as intestinal-type, while those without glandular structures are referred to as diffuse-type carcinomas. Those with a mixed, solid or unusual appearance are regarded as unclassifiable/indeterminate.

- **The molecular features characterising intestinal-type and diffuse-type gastric cancer suggest that the different histological phenotype is related to a different underlying genetic phenotype and most likely different aetiology.**

- **Abnormalities of the CDH1 (Ecadherin) gene and aberrant expression of this protein have been found in up to 90% of sporadic gastric carcinomas, especially the diffuse type.** Germline CDH1 mutations are the defining molecular defect in hereditary diffuse gastric cancer.

- **The stomach is the commonest site for gastrointestinal lymphomas which are mostly B-cell non-Hodgkin’s lymphomas.** The most common lymphoma is low-grade MALT lymphoma thought to be initiated by *H. pylori* infection. Several different chromosomal translocations have been identified, some of them conferring therapy resistance.

- **Three subgroups of patients with neuroendocrine tumours (formerly called ‘carcinoids’) can be identified.** Most are benign and associated with overgrowth of the ECL cells. Solitary lesions frequently metastasise.
Key references


