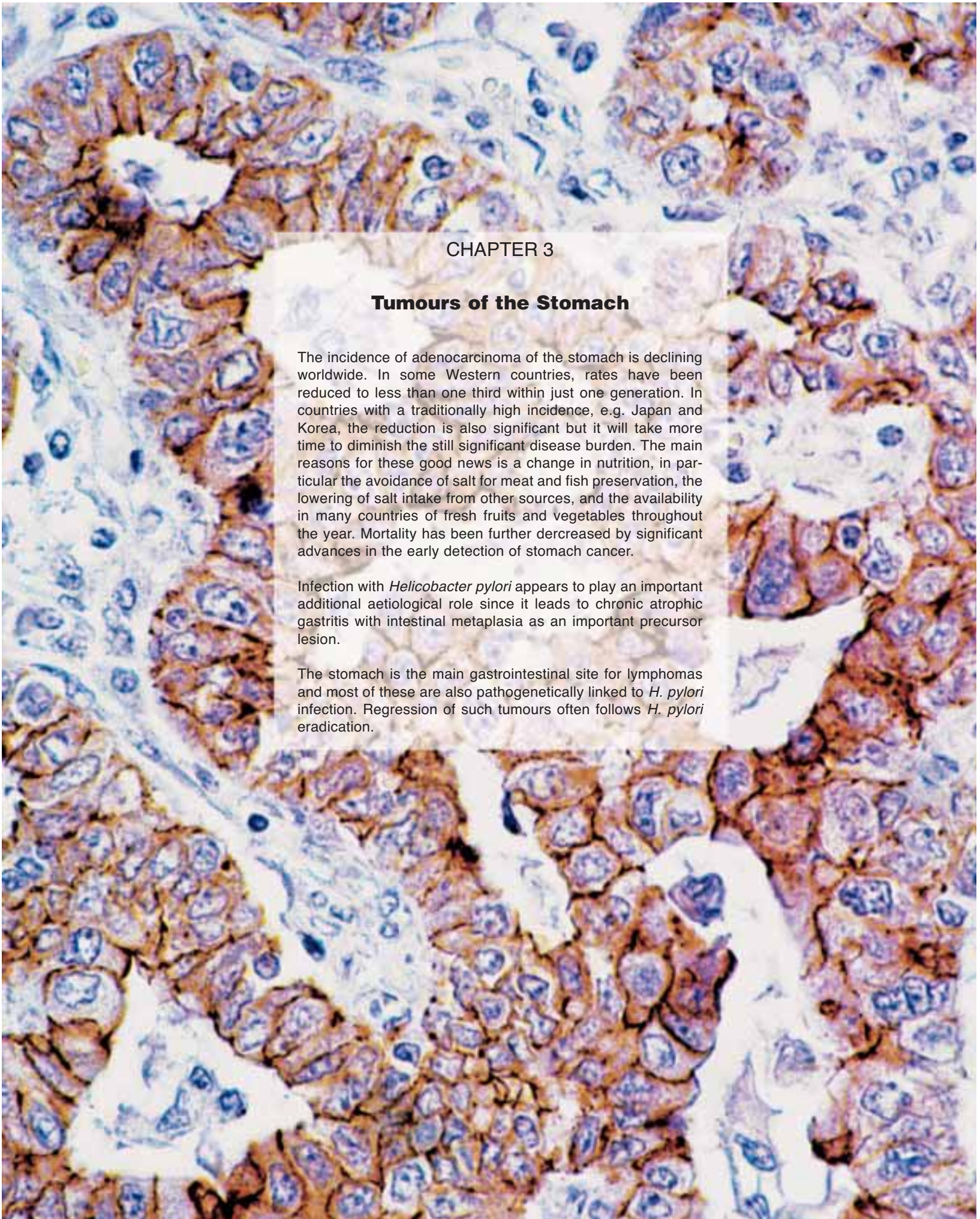

CHAPTER 3

Tumours of the Stomach

The incidence of adenocarcinoma of the stomach is declining worldwide. In some Western countries, rates have been reduced to less than one third within just one generation. In countries with a traditionally high incidence, e.g. Japan and Korea, the reduction is also significant but it will take more time to diminish the still significant disease burden. The main reasons for these good news is a change in nutrition, in particular the avoidance of salt for meat and fish preservation, the lowering of salt intake from other sources, and the availability in many countries of fresh fruits and vegetables throughout the year. Mortality has been further dercreased by significant advances in the early detection of stomach cancer.

Infection with *Helicobacter pylori* appears to play an important additional aetiological role since it leads to chronic atrophic gastritis with intestinal metaplasia as an important precursor lesion.

The stomach is the main gastrointestinal site for lymphomas and most of these are also pathogenetically linked to *H. pylori* infection. Regression of such tumours often follows *H. pylori* eradication.

WHO histological classification of gastric tumours[1]

Epithelial tumours	
Intraepithelial neoplasia – Adenoma	8140/0[2]
Carcinoma	
Adenocarcinoma	8140/3
intestinal type	8144/3
diffuse type	8145/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3
Others	
Carcinoid (well differentiated endocrine neoplasm)	8240/3

Non-epithelial tumours	
Leiomyoma	8890/0
Schwannoma	9560/0
Granular cell tumour	9580/0
Glomus tumour	8711/0
Leiomyosarcoma	8890/3
GI stromal tumour	8936/1
benign	8936/0
uncertain malignant potential	8936/1
malignant	8936/3
Kaposi sarcoma	9140/3
Others	
Malignant lymphomas	
Marginal zone B-cell lymphoma of MALT-type	9699/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Others	

Secondary tumours

[1] The classification is modified from the previous WHO histological classification of tumours {2066} taking into account changes in our understanding of these lesions. In the case of endocrine neoplasms, the classification is based on the recent WHO clinicopathological classification {1784}, but has been simplified to be of more practical utility in morphological classification.

[2] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplaia grade III (8148/2), and adenocarcinoma in situ (8140/2).

TNM classification of gastric tumours

TNM classification[1]

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria or submucosa
T2	Tumour invades muscularis propria or subserosa[2]
T3	Tumour penetrates serosa (visceral peritoneum) without invasion of adjacent structures[2,3,4,5]
T4	Tumour invades adjacent structures[2,3,4,5]

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 6 regional lymph nodes
N2	Metastasis in 7 to 15 regional lymph nodes
N3	Metastasis in more than 15 regional lymph nodes

M – Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIA	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1, N2, N3	M0
	T1, T2, T3	N3	M0
	Any T	Any N	M1

[1] {1, 66}. This classification applies only to carcinomas.

[2] A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.

[3] A tumour may penetrate muscularis propria with extension into the gastrocolic or gastrohepatic ligaments or the greater and lesser omentum without perforation of the visceral peritoneum covering these structures. In this case, the tumour is classified as T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or omenta, the tumour is classified as T3.

[4] The adjacent structures of the stomach are the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

[5] Intramural extension to the duodenum or oesophagus is classified by the depth of greatest invasion in any of these sites including stomach.

Gastric carcinoma

C. Fenoglio-Preiser
F. Carneiro
P. Correa
P. Guilford
R. Lambert
F. Megraud
N. Muñoz
S.M. Powell
M. Rugge
M. Sasako
M. Stolte
H. Watanabe

Definition

A malignant epithelial tumour of the stomach mucosa with glandular differentiation. Its aetiology is multifactorial; most commonly it develops after a long period of atrophic gastritis.

Tumours of the oesophagogastric junction are dealt with in the preceding chapter.

ICD-O codes

Adenocarcinoma	8140/3
Intestinal type	8144/3
Diffuse type	8145/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3

Epidemiology

Geographical distribution

Gastric cancer was the second commonest cancer in the world in 1990, with an estimated 800,000 new cases and 650,000 deaths per year; 60% of them occurred in developing countries {1469}. The areas with the highest incidence rates (> 40/100,000 in males) are in Eastern Asia, the Andean regions of South America and Eastern Europe. Low rates (< 15/100,000) are found in North America, Northern Europe, and most countries in Africa and in Southeastern Asia {1471}. There is about a 20-fold difference in the incidence rates when comparing the rates in Japan with those of some white populations from the US and those of some African countries. A predominance of the intestinal type of adenocarcinoma occurs in high-risk areas, while the diffuse type is relatively more common in low-risk areas {1296}.

Time trends

A steady decline in the incidence and mortality rates of gastric carcinoma has been observed worldwide over the past several decades, but the absolute number of new cases per year is increasing mainly because of the aging of the population {1296}. Analysis of time trends by histological types indicates that the incidence decline results from a decline in the intestinal type of carcinoma {1296}.

Age and sex distribution

Gastric carcinoma is extremely rare below the age of 30; thereafter it increases rapidly and steadily to reach the highest rates in the oldest age groups, both in males and females. The intestinal type rises faster with age than the diffuse type; it is more frequent in males than in females.

Diffuse carcinoma tends to affect younger individuals, mainly females; it frequently has hereditary characteristics, perhaps modulated by environmental influences {1738, 1633}.

Aetiology

Diet

Epidemiological studies in different populations show that the most consistent association is diet. This is especially true of intestinal type carcinomas. An adequate intake of fresh fruits and vegetables lowers the risk {1450}, due to their antioxidant effects. Ascorbic acid, carotenoids, folates and tocopherols are considered active ingredients. Salt intake strongly associates with the risk of gastric carcinoma and its precursor lesions {869}.

Other foods associated with high risk in some populations include smoked or cured meats or fish, pickled vegetables and chili peppers.

Alcohol, tobacco and occupational exposures to nitrosamines and inorganic dusts have been studied in several populations, but the results have been inconsistent.

Bile reflux

The risk of gastric carcinoma increases 5-10 years after gastric surgery, especially when the Bilroth II operation, which increases bile reflux, was performed.

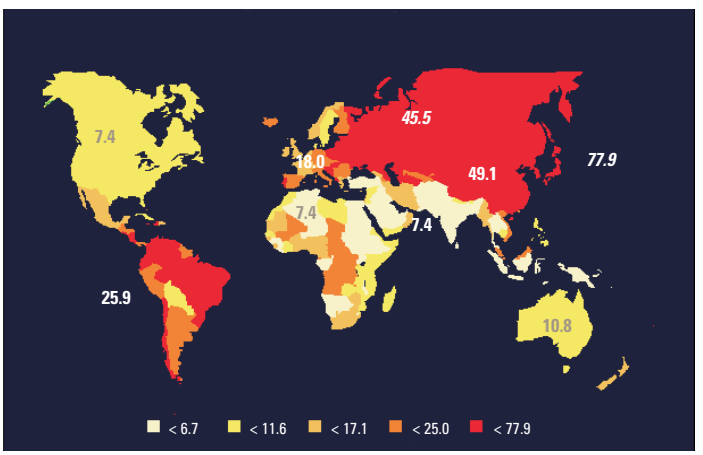

Fig. 3.01 Worldwide annual incidence (per 100,000) of stomach cancer in males. Numbers on the map indicate regional average values.

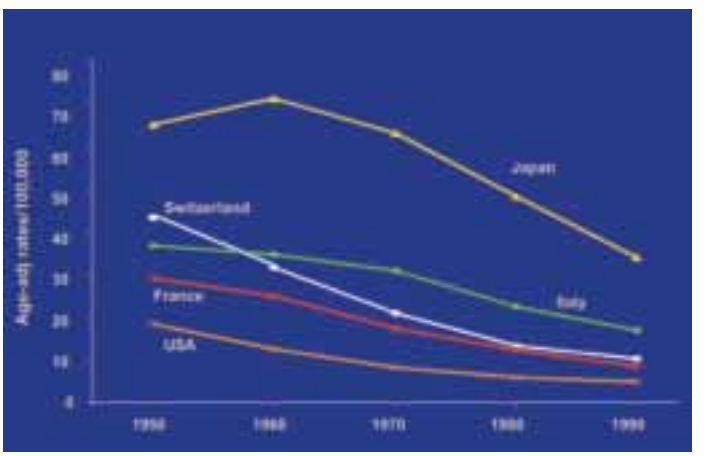

Fig. 3.02 The mortality of stomach cancer is decreasing worldwide, including countries with a high disease burden.

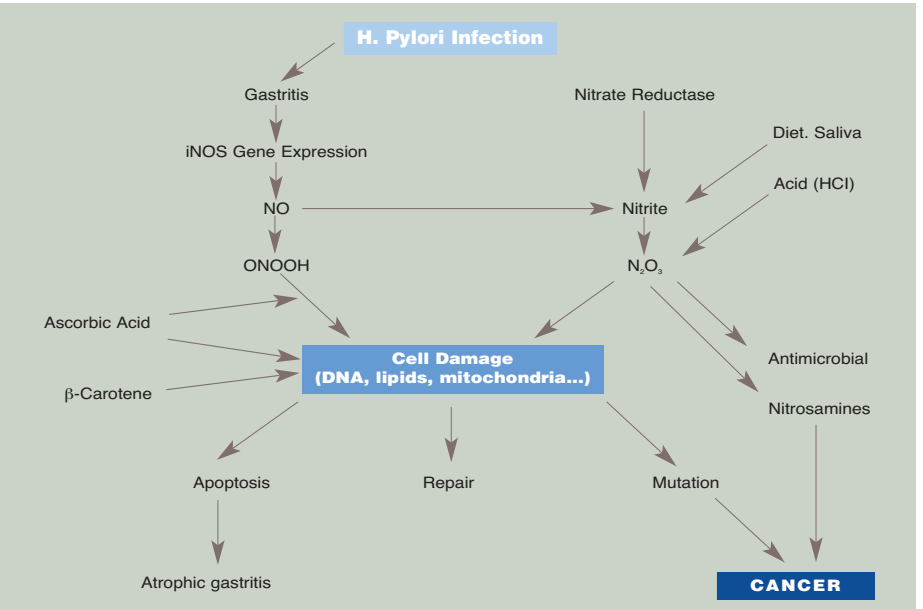

Fig. 3.03 Pathogenetic scheme of carcinogenesis in the stomach.

Helicobacter pylori infection

The most important development in the epidemiology of adenocarcinoma is the recognition of its association with *Helicobacter pylori* infection. Strong epidemiological evidence came from three independent prospective cohort studies reporting a significantly increased risk in subjects who 10 or more years before the cancer diagnosis had anti-*H. pylori* antibodies, demonstrable in stored serum samples {1371, 1473, 519}. At the pathological level, *H. pylori* has been shown to induce the phenotypic changes leading up to the development of adenocarcinoma (i.e. mucosal atrophy, intestinal metaplasia and dysplasia) in both humans and in experimental animals {1635, 350, 2069}.

A prolonged precancerous process, lasting decades, precedes most gastric cancers. It includes the following sequential steps: chronic gastritis, multifocal atrophy, intestinal metaplasia, and intraepithelial neoplasia {342}. Gastritis and atrophy alter gastric acid secretion, elevating gastric pH, changing the flora and allowing anaerobic bacteria to colonize the stomach. These bacteria produce active reductases that transform food nitrate into nitrite, an active molecule capable of reacting with amines, amides and ureas to produce carcinogenic N-nitroso compounds {2167}.

H. pylori acts as a gastric pathogen and it is important in several steps in the carcinogenic cascade. *H. pylori* is the most frequent cause of chronic gastritis. It decreases acid-pepsin secretion and interferes with anti-oxidant functions by decreasing intragastric ascorbic acid (AA) concentrations. The organisms predominantly occur in the mucus layer overlying normal gastric epithelium. They are absent in areas overlying intestinal metaplasia where neoplasia originates. Thus, *H. pylori's* carcinogenic influences are exerted from a distance, via soluble bacterial products or the inflammatory response generated by the infection.

H. pylori genome. H. pylori is genetically heterogeneous, and all strains may not play the same role in the development of malignancy. Strains containing a group of genes named cag pathogenicity island {264} induce a greater degree of inflammation than strains lacking these genes. The mechanism involves epithelial production of interleukin 8 via a nuclear factor KappaB pathway. There is an association between an infection with a cag positive *H. pylori* strain and the development of gastric carcinoma {1549}.

The determination of the complete DNA sequence of two *H. pylori* strains has shown other similar 'islands' are also present in the *H. pylori* genome. Research is ongoing to determine whether strain-specific genes located in one of these islands named the plasticity zone, or outside on the rest of the chromosome, could be associated with gastric carcinogenesis. *H. pylori* can also produce a vacuolating cytotoxin named VacA. This cytotoxin, responsible for epithelial cell damage, also associates with gastric carcinogenesis {1771}. The aetiological role of *H. pylori* in gastric carcinogenesis was confirmed when inoculation of a cag and VacA positive strain was able to induce intestinal metaplasia and gastric carcinoma in Mongolian gerbils {2069}.

Excessive cell proliferation. Cell replication, a requisite of carcinogenesis, potentiates action of carcinogens targeting DNA. The higher the replication rate, the greater the chance that replication errors become fixed and expressed in subsequent cell generations. Spontaneous mutations lead to subsequent neoplastic transformation, but whether or not they cause epidemic increases in cancer rates is debatable. The latter is better explained by the presence of external or endogenous carcinogens. Proliferation is higher in *H. pylori* infected than in non-infected stomachs; it declines significantly after infection eradication {187} supporting the mitogenic influence of *H. pylori* on gastric epithelium. Ammonia, a substance stimulating cell replication, is abundantly liberated by the potent urease activity of *H. pylori* in the immediate vicinity of gastric epithelium.

Oxidative stress. Gastritis is associated with increased production of oxidants and reactive nitrogen intermediates, including nitric oxide (NO). There is an increased expression of the inducible isoform of nitric oxide synthase in gastritis {1157}. This isoform causes continuous production of large amounts of NO. NO can also be generated in the gastric lumen from non-enzymatic sources. Acidification of nitrite to NO produces the reactive nitrogen species dinitrogen trioxide (N2O3), a potent nitrosating agent that forms nitrosothiols and nitrosamines {628}. Nitrosated compounds are recognized gastric carcinogens in the experimental setting.

Interference with antioxidant functions. Ascorbic acid (AA), an antioxidant, is actively transported from blood to the gastric lumen by unknown mechanisms. Its putative anti-carcinogenic role is by preventing oxidative DNA damage. *H. pylori* infected individuals have lower AA intragastric concentrations than non-infected subjects. Following *H. pylori*

treatment, intragastric AA concentrations increase to levels resembling those of non-infected individuals {1613}.

DNA damage. Free radicals, oxidants and reactive nitrogen species all cause DNA damage {344}. These usually generate point mutations, the commonest being G:C→A:T, the commonest type of transformation in cancer with a strong link to chemical carcinogenesis. Peroxynitrite forms nitro-guanine adducts that induce DNA damage, generating either DNA repair or apoptosis. The latter process removes cells containing damaged DNA from the pool of replicating cells in order to avoid introduction of mutations into the genome and an associated heightened cancer risk. NO impairs DNA repair by compromising the activity of Fpg, a DNA repair protein. Thus, NO not only causes DNA damage but it also impairs repair mechanisms designed to prevent the formation of genetic mutations.

As noted, cell proliferation increases in *H. pylori* infection. This increased replication is balanced by increased cell death. It is likely that the increased mitoses are a response to increased epithelial loss. However, the replicative rate exceeds apoptotic rates in patients infected with the virulent cagA vacA s1a *H. pylori* {1481} suggesting that cell loss also occurs via desquamation in patients infected by toxigenic *H. pylori* strains. Antitoxin derived from *H. pylori* also induces apoptosis. In patients with *H. pylori* gastritis, treatment with anti-oxidants attenuates the degree of apoptosis and peroxynitrite formation {1481}.

It seems more than coincidental that dietary nitrite, nitrosamines and *H. pylori*-induced gastritis share so much chemistry and their association with cancer. As this process is chronic, the opportunity for random hits to the genome to occur at critical sites increases dramatically.

Localization

The most frequent site of sub-cardial stomach cancer is the distal stomach, i.e. the antro-pyloric region. Carcinomas in the body or the corpus of the stomach are typically located along the greater or lesser curvature.

Clinical features

Symptoms and signs

Early gastric cancer often causes no symptoms, although up to 50% of patients may have nonspecific gastrointestinal complaints such as dyspepsia. Among patients in Western countries who have endoscopic evaluations for dyspepsia, however, gastric carcinoma is found in only 1-2% of cases (mostly in men over the age of 50). Symptoms of advanced carcinoma include abdominal pain that is often persistent and unrelieved by eating. Ulcerated tumours may cause bleeding and haematemesis, and tumours that obstruct the gastric outlet may cause vomiting. Systemic symptoms such as anorexia and weight loss suggest disseminated disease.

The lack of early symptoms often delays the diagnosis of gastric cancer. Consequently, 80- 90% of Western patients with gastric cancers present to the physician with advanced tumours that have poor rates of curability. In Japan, where gastric cancer is common, the government has encouraged mass screening of the adult population for this tumour. Approximately 80% of gastric malignancies detected by such screening programs are early gastric cancers. However, many individuals do not choose to participate in these screening programs, and consequently only approximately 50% of all gastric cancers in Japan are diagnosed in an early stage.

Imaging and endoscopy

Endoscopy is widely regarded as the most sensitive and specific diagnostic test for gastric cancer. With high resolution endoscopy, it is possible to detect slight changes in colour, relief, and architecture of the mucosal surface that suggest early gastric cancer. Endoscopic detection of these early lesions can be improved with chromoendoscopy (e.g. using indigo carmine solution at 0.4 %). Even with these procedures, a substantial number of early gastric cancers can be missed {745A}.

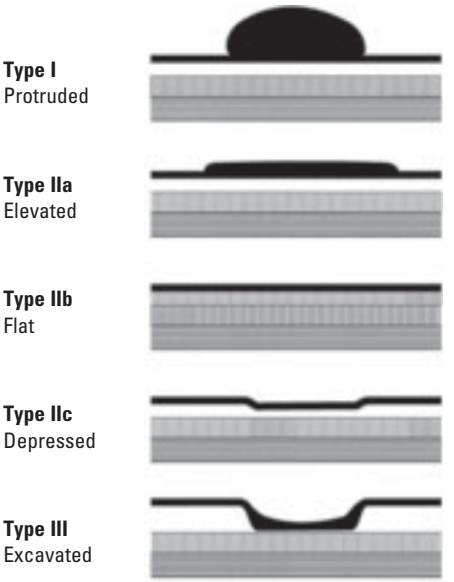

Fig. 3.04 Growth features of early gastric carcinoma.

Gastric cancers can be classified endoscopically according to the growth pattern {1298, 63} The patterns I. II and III of superficial cancer (Fig. 3.03) reflect the gross morphology of the operative specimen. The risk of deep and multifocal penetration into the submucosa and the risk of lymphatic invasion is higher in type IIc, the depressed variant of type II. Infiltration of the gastric wall (linitis plastica) may not be apparent endoscopically. This lesion may be suspected if there is limited flexibility of the gastric wall. Diagnosis may require multiple, jumbo biopsies. The depth of invasion of the tumour is staged with endoscopic ultrasound. A 5-layer image is obtained at 7.5/12 MHz: in superficial (T1) cancer the second hyperechoic layer is not interrupted.

Radiology with barium meal is still used in mass screening protocols in Japan, followed by endoscopy if an abnormality has been detected. For established gas-

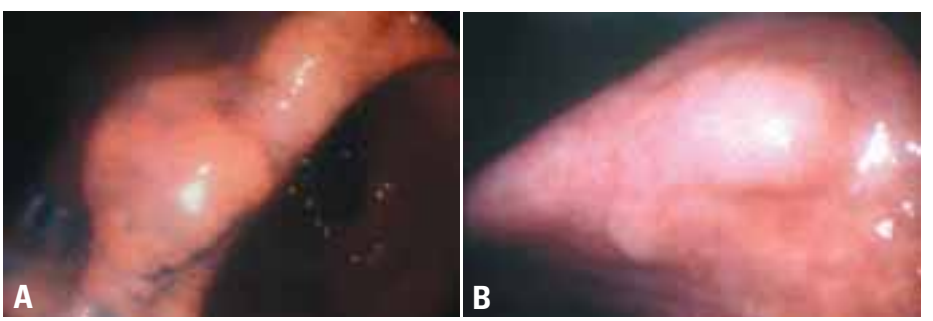

Fig. 3.05 Endoscopic views of early, well differentiated adenocarcinoma. **A** Polypoid type. **B** Elevated type.

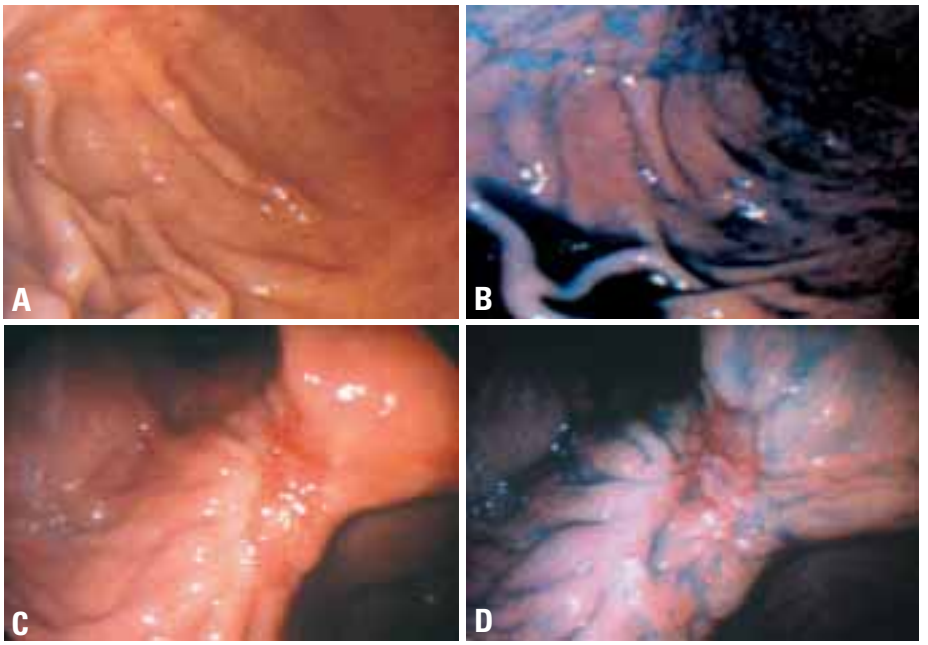

Fig. 3.06 Endoscopic views of gastric cancer **(A, C)** and corresponding images with dye enhancement **(B, D)**. **A, B** Depressed early gastric cancer. **C, D** Deep ulcer scar surrounded by superficial early gastric cancer infiltrating the mucosa and submucosa.

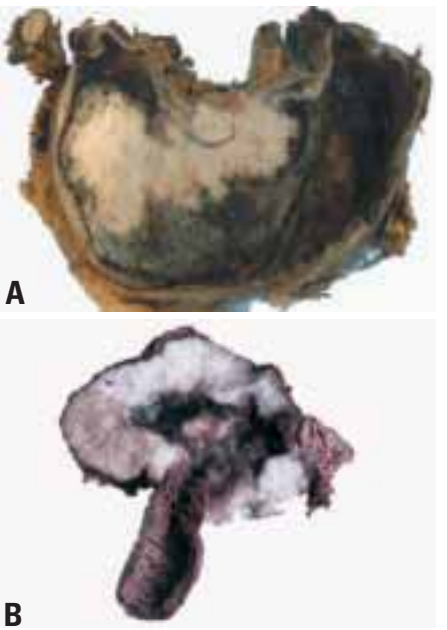

Fig. 3.08 Gastric adenocarcinoma of **(A)** polypoid and **(B)** diffusely infiltrative type.

tric cancers, radiology usually is not necessary, but may complement endoscopic findings in some cases. Tumour staging prior to treatment decision involves percutaneous ultrasound or computerized tomography to detect liver metastases and distant lymph node metastases. Laparoscopic staging may be the only way to exclude peritoneal seeding in the absence of ascites.

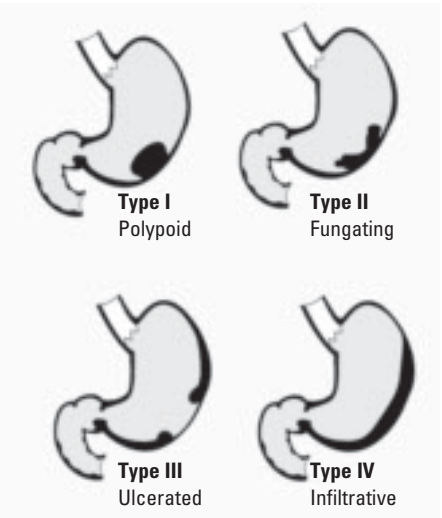

Fig. 3.07 Borrmann classification of advanced gastric carcinoma.

Macroscopy

Dysplasia may present as a flat lesion (difficult to detect on conventional endoscopy, but apparent on dye-staining endoscopy) or polypoid growth. Appearances intermediate between them include a depressed or reddish or discolored mucosa. The macroscopic type of early gastric carcinoma is classified using critera similar to those in endoscopy (Fig. 3.03) {1298, 63}. The gross appearance of advanced carcinoma forms the basis of the Borrmann classification (Fig. 3.06) {63, 175}.

Ulcerating types II or III are common. Diffuse (infiltrative) tumours (type IV) spread superficially in the mucosa and submucosa, producing flat, plaque-like lesions, with or without shallow ulcerations. With extensive infiltration, a linitis plastica or 'leather bottle' stomach results. Mucinous adenocarcinomas appear gelatinous with a glistening cut surface.

Tumour spread and staging

Gastric carcinomas spread by direct extension, metastasis or peritoneal dissemination. Direct tumour extension involves adjacent organs. Tumours invading the duodenum are most often of the diffuse type and the frequency of serosal, lymphatic, and vascular invasion and lymph node metastases in these lesions is high. Duodenal invasion may occur through the submucosa or subserosa or via the submucosal lymphatics.

Duodenal invasion occurs more frequently than expected based on gross examination. Therefore, resection margins should be monitored by intraoperative consultation.

Intestinal carcinomas preferentially metastasize haematogenously to the liver, whereas diffuse carcinomas preferentially metastasize to peritoneal surfaces {1273, 245}. An equal incidence of lymph node metastases occurs in both types of tumours with T2 or higher lesions. Mixed tumours exhibit the metastatic patterns of both intestinal and diffuse types. When carcinoma penetrates the serosa, peritoneal implants flourish. Bilateral massive ovarian involvement *(Krukenberg tumour)* can result from transperitoneal or haematogenous spread.

The principal value of nodal dissection is the detection and removal of metastatic disease and appropriate tumour staging. The accuracy of pathological staging is proportional to the number of regional lymph nodes examined and their location. When only nodes close to the tumour are assessed, many cancers are classified incorrectly.

Histopathology

Gastric adenocarcinomas are either gland-forming malignancies composed

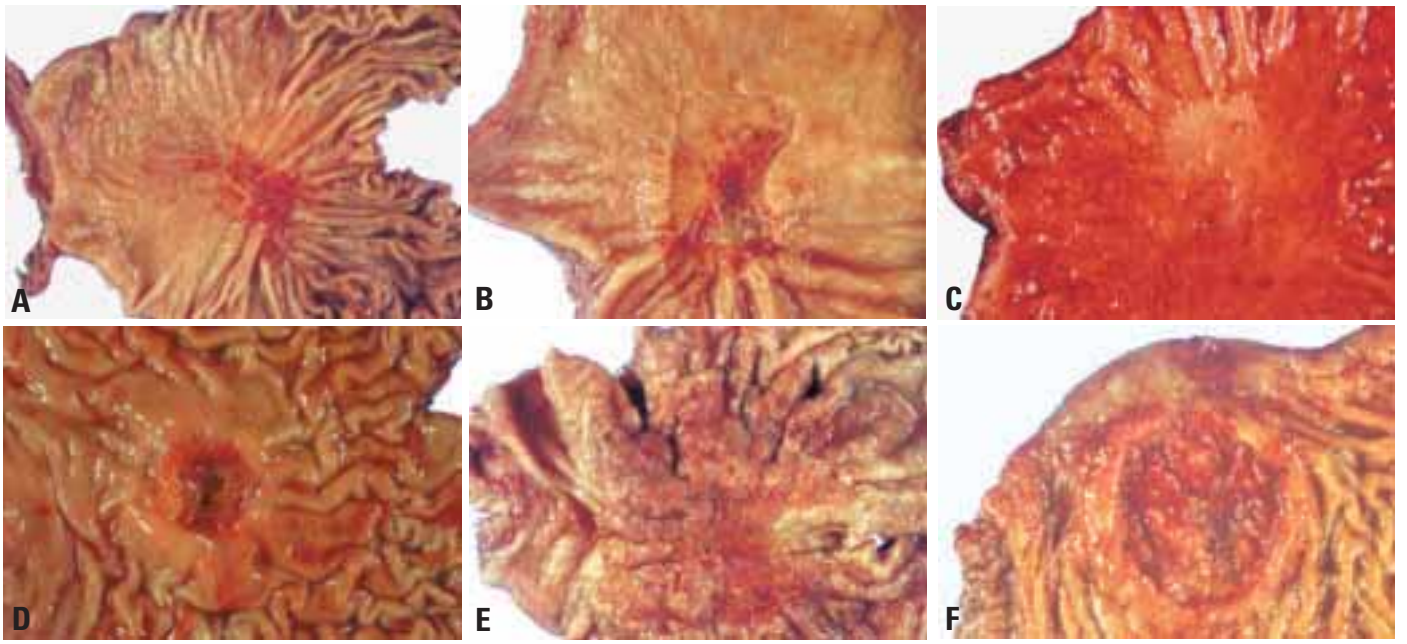

Fig. 3.09 **A** Depressed adenocarcinoma. **B** Depressed signet ring cell carcinoma. **C** Gastric cancer, dye sprayed (pale area). **D, E, F** Advanced gastric carcinoma with varying degrees of infiltration.

of tubular, acinar or papillary structures, or they consist of a complex mixture of discohesive, isolated cells with variable morphologies, sometimes in combination with glandular, trabecular or alveolar solid structures {243}. Several classification systems have been proposed, including Ming, Carniero, and Goseki {1623}, but the most commonly used are those of WHO and Laurén {419, 87}.

WHO classification

Despite their histological variability, usually one of four patterns predominates. The diagnosis is based on the predominant histological pattern.

Tubular adenocarcinomas

These contain prominent dilated or slit-like and branching tubules varying in their diameter; acinar structures may be present. Individual tumour cells are columnar, cuboidal, or flattened by intraluminal mucin. Clear cells may also be present. The degree of cytological atypia varies from low to high-grade {466, 1362}. A poorly differentiated variant is sometimes called *solid carcinoma.* Tumours with a prominent lymphoid stroma are sometimes called *medullary carcinomas or carcinomas with lymphoid stroma* {2063}. The degree of desmoplasia varies and may be conspicuous.

Papillary adenocarcinomas

These are well-differentiated exophytic carcinomas with elongated finger-like processes lined by cylindrical or cuboidal cells supported by fibrovascular connective tissue cores. The cells tend to maintain their polarity. Some tumours show tubular differentiation (papillotubular). Rarely, a micropapillary architecture is present. The degree of cellular atypia and mitotic index vary; there may be severe nuclear atypia. The invading tumour edge is usually sharply demarcated from surrounding structures; the tumour may be infiltrated by acute and chronic inflammatory cells.

Mucinous adenocarcinomas

By definition, > 50% of the tumour contains extracellular mucinous pools. The two major growth patterns are (1) glands lined by a columnar mucous-secreting epithelium together with interstitial mucin and (2) chains or irregular cell clusters floating freely in mucinous lakes. There may also be mucin in the interglandular stroma. Scattered signet-ring cells, when present, do not dominate the histological picture. Grading mucinous adenocarci-

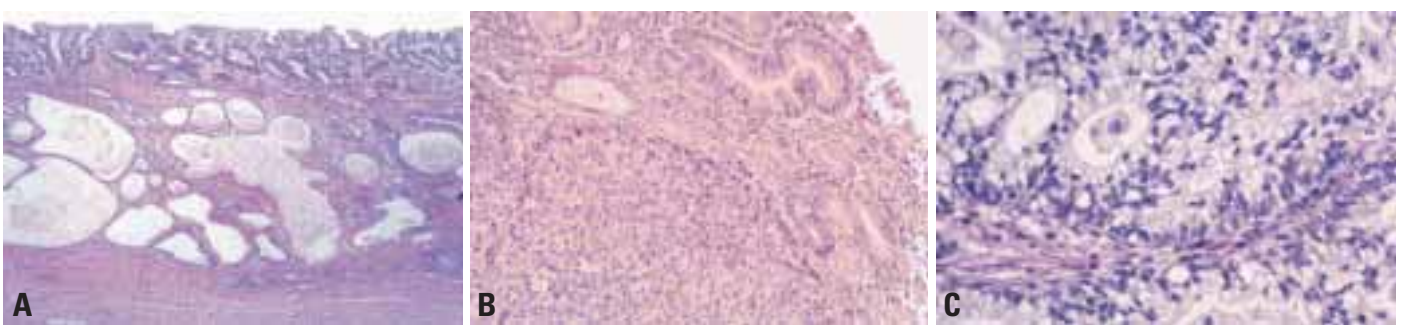

Fig. 3.10 Features of tubular adenocarcinoma. **A** Well differentiated tumour with invasion into the muscularis propria. **B** Solid variant. **C** Clear cell variant.

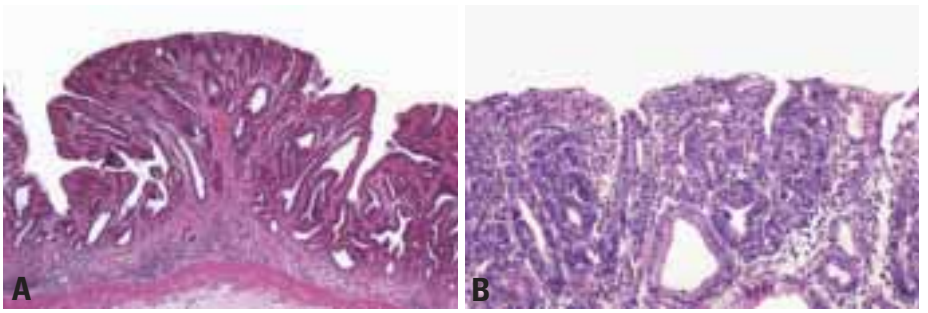

Fig. 3.11 **A, B** Tubular adenocarcinoma.

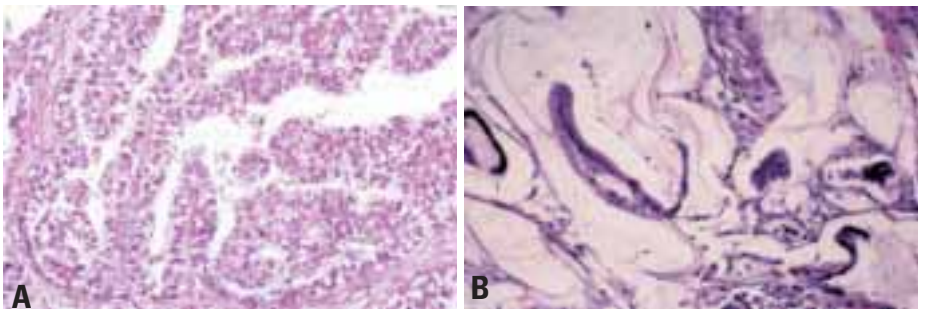

Fig. 3.12 **A** Papillary adenocarcinoma. **B** Well differentiated mucinous adenocarcinoma.

nomas is unreliable in tumours containing only a few cells. The term 'mucin-producing' is not synonymous with mucinous in this context.

Signet-ring cell carcinomas

More than 50% of the tumour consists of isolated or small groups of malignant cells containing intracytoplasmic mucin. Superficially, cells lie scattered in the lamina propria, widening the distances between the pits and glands. The tumour cells have five morphologies: (1) Nuclei push against cell membranes creating a classical signet ring cell appearance due to an expanded, globoid, optically clear cytoplasm. These contain acid mucin and stain with Alcian blue at pH 2.5; (2) other diffuse carcinomas contain cells with central nuclei resembling histiocytes, and show little or no mitotic activity; (3) small, deeply eosinophilic cells with prominent, but minute, cytoplasmic granules containing neutral mucin; (4) small cells with little or no mucin, and (5) anaplastic cells with little or no mucin. These cell types intermingle with one another and constitute varying tumour proportions. Signet-ring cell tumours may also form lacy or delicate trabecular glandular patterns and they may display a zonal or solid arrangement.

Signet-ring cell carcinomas are infiltrative; the number of malignant cells is comparatively small and desmoplasia may be prominent. Special stains, including mucin stains (PAS, mucicarmine, or Alcian blue) or immunohistochemical staining with antibodies to cytokeratin, help detect sparsely dispersed tumour cells in the stroma. Cytokeratin immunostains detect a greater percentage of neoplastic cells than do mucin stains. Several conditions mimic signet-ring cell carcinoma including signet-ring lymphoma, lamina propria muciphages, xanthomas and detached or dying cells associated with gastritis.

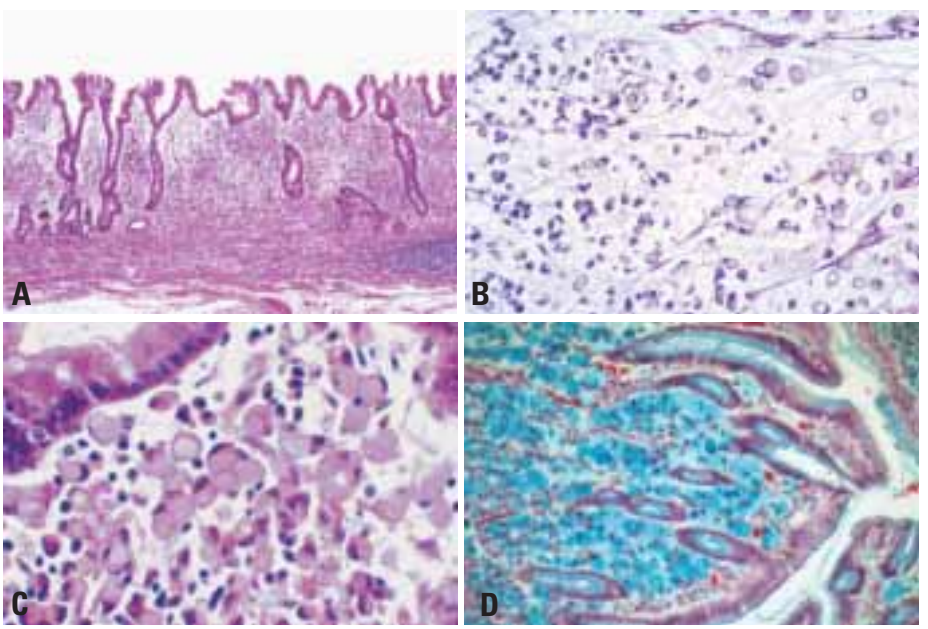

Fig. 3.13 Signet-ring cell carcinomas. **A** Overview showing Infiltration of the lamina propria. **B** Dispersed signet-ring cells. **C** Accumulation of neoplastic signet ring cells in the mucosa. **D** Alcian green positive signet-ring cells expanding the lamina propria in this Movat stain.

Laurén classification

The Laurén classification {1021} has proven useful in evaluating the natural history of gastric carcinoma, especially with regard to its association with environmental factors, incidence trends and its precursors. Lesions are classified into one of two major types: intestinal or diffuse. Tumours that contain approximately equal quantities of intestinal and diffuse components are called *mixed carcinomas*. Carcinomas too undifferentiated to fit neatly into either category are placed in the *indeterminate* category.

Intestinal carcinomas

These form recognizable glands that range from well differentiated to moderately differentiated tumours, sometimes with poorly differentiated tumour at the advancing margin. They typically arise on a background of intestinal metaplasia. The mucinous phenotype of these cancers is intestinal, gastric and gastrointestinal.

Diffuse carcinomas

They consist of poorly cohesive cells diffusely infiltrating the gastric wall with little

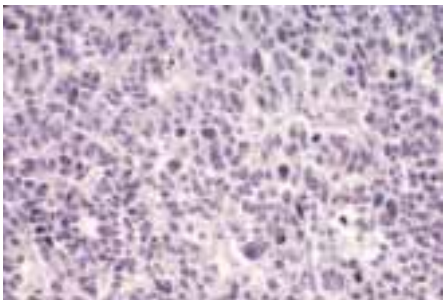

Fig. 3.14 Undifferentiated gastric carcinoma.

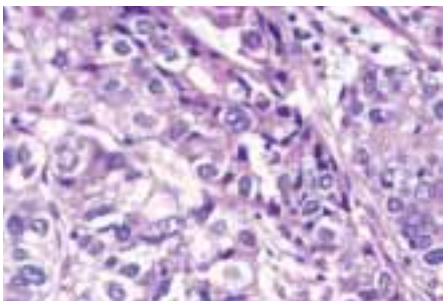

Fig. 3.15 Hepatoid variant of gastric carcinoma.

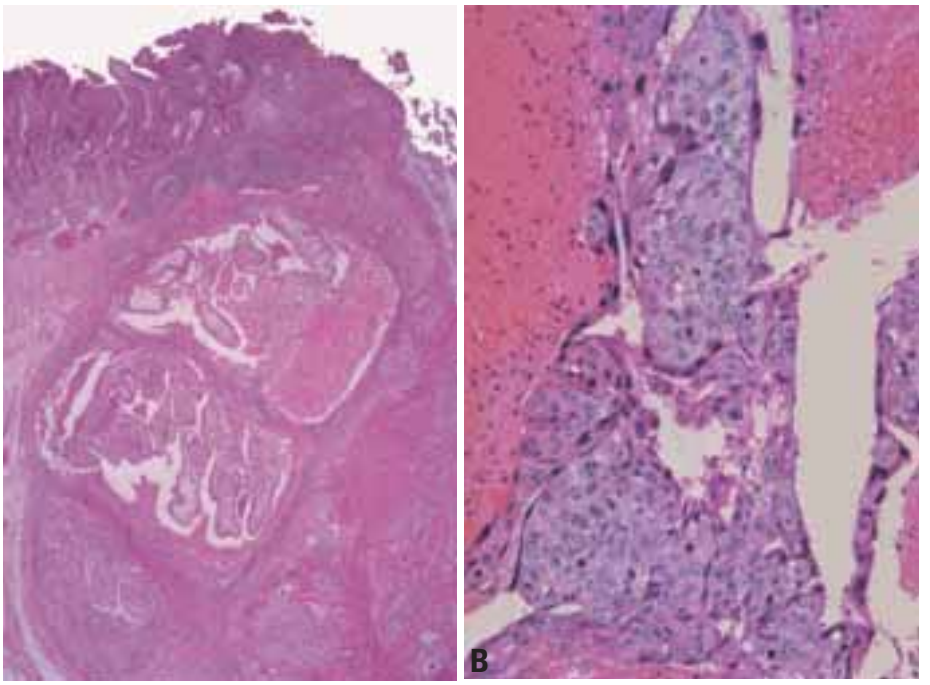

Fig. 3.16 Gastric choriocarcinoma composed of syncytiotrophoblastic and cytotrophoblastic cells next to thin-walled vascular structures. **A** Papillary carcinoma component is adjacent to the choriocarcinoma. **B** High magnification of the choriocarcinoma.

or no gland formation. The cells usually appear round and small, either arranged as single cells or clustered in abortive, lacy gland-like or reticular formations. These tumours resemble those classified as signet-ring cell tumours in the WHO classification. The mitotic rate is lower in diffuse carcinomas than in intestinal tumours. Small amounts of interstitial mucin may be present. Desmoplasia is more pronounced and associated inflammation is less evident in diffuse cancers than in the intestinal carcinomas.

Rare variants

Several other carcinomas exist that are not an integral part of the Laurén or WHO classifications.

Adenosquamous carcinoma

This lesion combines an adenocarcinoma and squamous cell carcinoma; neither quantitatively prevails. Transitions exist between both components. A tumour with a distinct boundary between the two components may represent a *collision tumour.* Tumours containing discrete foci of benign-appearing squamous metaplasia are termed adenocarcinomas with *squamous differentiation* (synonymous with adenoacanthoma).

Squamous cell carcinoma

Pure squamous cell carcinomas develop rarely in the stomach; they resemble squamous cell carcinomas arising elsewhere in the body.

Undifferentiated carcinoma

These lesions lack any differentiated features beyond an epithelial phenotype (e.g. cytokeratin expression). They fall into the indeterminate group of Laurén's scheme. Further analysis of this heterogeneous group using histochemical methods may allow their separation into other types.

Other rare tumours include mixed adenocarcinoma-carcinoid (mixed exocrine-endocrine carcinoma), small cell carcinoma, parietal cell carcinoma, choriocarcinoma, endodermal sinus tumour, embryonal carcinoma, Paneth cell rich-adenocarcinoma and hepatoid adenocarcinoma.

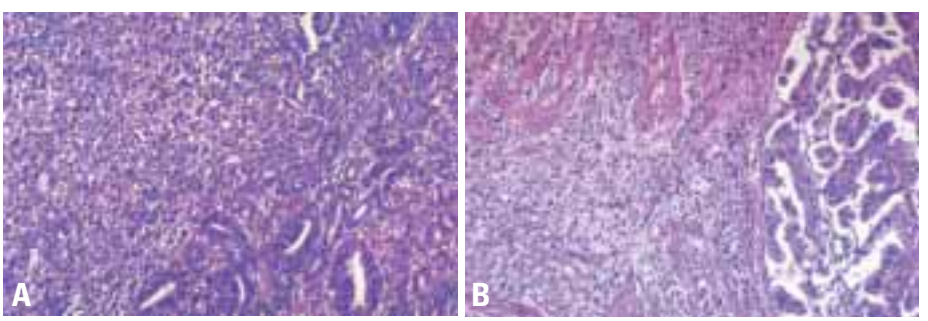

Fig. 3.17 A, B Adenocarcinoma, poorly differentiated. These two lesions show both intestinal and diffuse components (Laurén classification).

Early gastric cancer

Early gastric cancer (EGC) is a carcinoma limited to the mucosa or the mucosa and submucosa, regardless of nodal status. Countries in which asymptomatic patients are screened have a high incidence of EGCs ranging from 30-50% {1410, 908, 718}, contrasting with a smaller fraction of 16-24% {620, 253, 627} in Western countries. The follow-up of dysplastic lesions does appear to increase the prevalence of EGC. The cost effectiveness of such an integrated

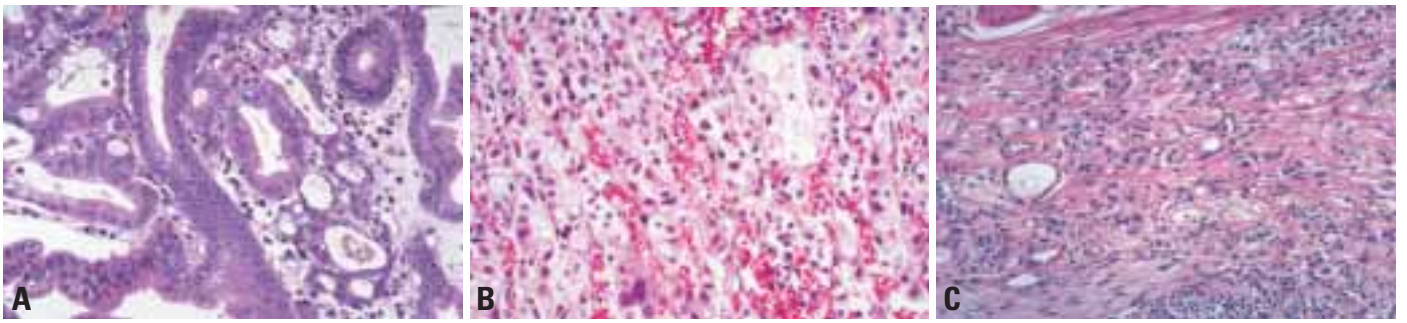

Fig. 3.18 Tubular adenocarcinoma. **A** Well differentiated; intramucosal invasion. **B** Moderately differentiated. **C** Poorly differentiated.

endoscopic/biopsy approach remains to be evaluated {1634, 1638}. Histologically, most subtypes of carcinoma occur in EGC in either pure or mixed forms. Elevated carcinomas with papillary, granular or nodular patterns and a red colour are more often well or moderately differentiated, tubular or papillary tumours with intestinal features; sometimes a pre-existing adenoma is recognizable. Flat, depressed, poorly differentiated carcinomas may contain residual or regenerative mucosal islands. Ulcerated lesions are either intestinal or diffuse cancers.

Adenocarcinoma limited to the mucosal thickness has also been divided into small mucosal (< 4cm=SM) and superficial (> 4cm=SUPER) {950}. Both of them may be strictly confined at the mucosal level (small mucosal M and superficial M) or focally infiltrate the sub-mucosa (small mucosal SM and superficial SM). In the penetrating variant, (including two sub-categories: PenA and PenB) the invasion of the submucosa is more extensive than in the two above-mentioned variants. PenA is defined by a pushing margin, and is less frequent than PenB, which penetrates muscularis mucosae at multiple sites.

The prognosis is worse in PenA carcinomas (in contrast to adenocarcinomas of the colon, where a pushing margin is associated with a better prognosis). The coexistence of more than one of the described patterns results in the mixed variant {950}.

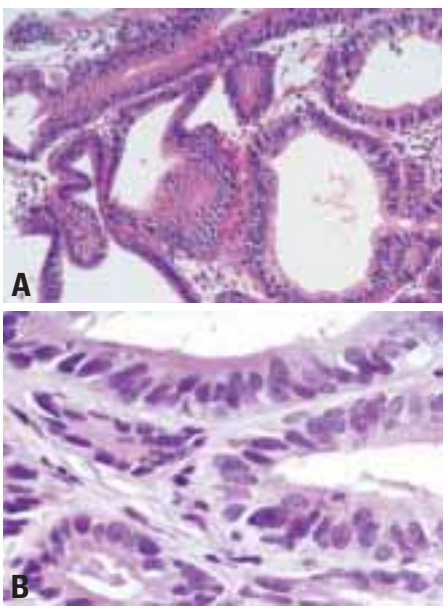

Fig. 3.19 A, B Tubular adenocarcinoma, well differentiated.

Stromal reactions

The four common stromal responses to gastric carcinoma are marked desmoplasia, lymphocytic infiltrates, stromal eosinophilia and a granulomatous response. The granulomatous reaction is characterized by the presence of single and confluent small sarcoid-like granulomas, often accompanied by a moderately intense mononuclear cell infiltrate. The lymphoid response is associated with an improved survival.

Grading

Well differentiated: An adenocarcinoma with well-formed glands, often resembling metaplastic intestinal epithelium.

Moderately differentiated: An adenocarcinoma intermediate between well differentiated and poorly differentiated.

Poorly differentiated: An adenocarcinoma composed of highly irregular glands that are recognized with difficulty, or single cells that remain isolated or are arranged in small or large clusters with mucin secretions or acinar structures. They may also be graded as *low-grade* (well and moderately differentiated) or *high-grade* (poorly differentiated). Note that this grading system applies primarily to tubular carcinomas. Other types of gastric carcinoma are not graded.

Precursor lesions

Gastritis and intestinal metaplasia

Chronic atrophic gastritis and intestinal metaplasia commonly precede and/or accompany intestinal type adenocarcinoma, particularly in high-incidence areas {780}. *H. pylori* associated gastritis is the commonest gastric precursor lesion.

However, autoimmune gastritis also associates with an increased carcinoma risk. If gastritis persists, gastric atrophy occurs followed by intestinal metaplasia, beginning a series of changes that may result in neoplasia, especially of intestinal type cancers. In contrast, diffuse gastric cancers often arise in a stomach lacking atrophic gastritis with intestinal metaplasia.

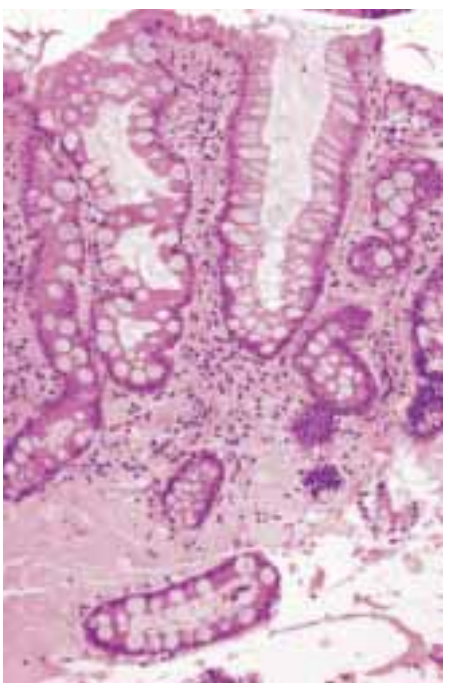
Fig. 3.20 Intestinal metaplasia. The two glands on the left exhibit complete intestinal metaplasia, others show the incomplete type.

There are two main types of intestinal metaplasia: 'complete' (also designated as 'small intestinal type' or type I), and 'incomplete' (types II and III) {843}. Different mucin expression patterns characterize the metaplasias: complete shows decreased expression of 'gastric' (MUC1, MUC5AC and MUC6) mucins and expression of MUC2, an intestinal mucin. In incomplete intestinal metaplasia, 'gastric' mucins are co-expressed with MUC2 mucin. These findings show that incomplete intestinal metaplasia has a mixed gastric and intestinal phenotype reflecting an aberrant differentiation program not reproducing any normal adult gastrointestinal epithelial phenotype {1574}.

Intraepithelial neoplasia

Intraepithelial neoplasia (dysplasia) arises in either the native gastric or of intestinalized gastric epithelia. *Pyloric gland adenoma* is a form of intraepithelial neoplasia arising in the native mucosa {2066, 1885}. In the multi-stage theory of gastric oncogenesis, intraepithelial neoplasia lies between atrophic metaplastic lesions and invasive cancer (Table 3.01).

Problems associated with diagnosing gastric intraepithelial neoplasia include the distinction from reactive or regenerative changes associated with active inflammation, and the distinction between intraepithelial and invasive carcinoma {1683, 1025}. Several proposals have been made for the terminology of the morphological spectrum of lesions that lie between non-neoplastic changes and early invasive cancer, including the recent international Padova classification {1636}.

Indefinite for intraepithelial neoplasia

Sometimes, doubts arise as to whether a lesion is neoplastic or non-neoplastic (i.e. reactive or regenerative), particularly in small biopsies. In such cases, the dilemma is usually solved by cutting deeper levels of the block, by obtaining additional biopsies, or after removing possible sources of cellular hyperproliferation. One important source of a potentially alarming lesion is the regeneration associated with NSAID-induced injury or superficial erosion/ulceration caused by gastric acid. Cases lacking all the attributes required for a definitive diagnosis of intraepithelial neoplasia may be placed into the category 'indefinite for intraepithelial neoplasia'.

In native gastric mucosa, foveolar hyperproliferation may be indefinite for dysplasia, showing irregular and tortuous tubular structures with epithelial mucus depletion, a high nuclear-cytoplasmic ratio and loss of cellular polarity. Large, oval/round, hyperchromatic nuclei associate with prominent mitoses, usually located near the proliferative zone in the mucous neck region.

In intestinal metaplasia, areas indefinite for intraepithelial neoplasia exhibit a hyperproliferative metaplastic epithelium. The glands may appear closely packed, lined by cells with large, hyperchromatic, rounded or elongated, basally located nuclei. Nucleoli are an inconsistent finding. The cyto-architectural alterations tend to decrease from the base of the glands to their superficial portion.

Intraepithelial neoplasia

It has flat, polypoid, or slightly depressed growth patterns; the flat pattern may lack any endoscopic changes on conventional endoscopy, but shows an irregular appearance on dye endoscopy. In Western countries, the term adenoma is applied when the proliferation produces a macroscopic, usually discrete, protruding lesion. However, in Japan, adenomas include all gross types (i.e. flat, elevated and depressed). Gastric adenomas are less common than hyperplastic polyps; overall, they account for approximately 10% of gastric polyps {1843}. They tend to arise in the antrum or mid stomach in areas of intestinal metaplasia.

Morphologically, adenomas can be described as tubular (the most common), tubulovillous, or villous; the latter two have also been called papillotubular and papillary. Most have epithelium of intestinal type, but some have gastric foveolar features.

Low-grade intraepithelial neoplasia

This lesion shows a slightly modified mucosal architecture, including the presence of tubular structures with budding and branching, papillary enfolding, crypt lengthening with serration, and cystic changes. Glands are lined by enlarged columnar cells with minimal or no mucin. Homogeneously blue vesicular, rounded or ovoid nuclei are usually pseudostratified in the proliferation zone located at the superficial portion of the dysplastic tubules.

High-grade intraepithelial neoplasia

There is increasing architectural distortion with glandular crowding and prominent cellular atypia. Tubules can be irregular in shape, with frequent branching and fold-

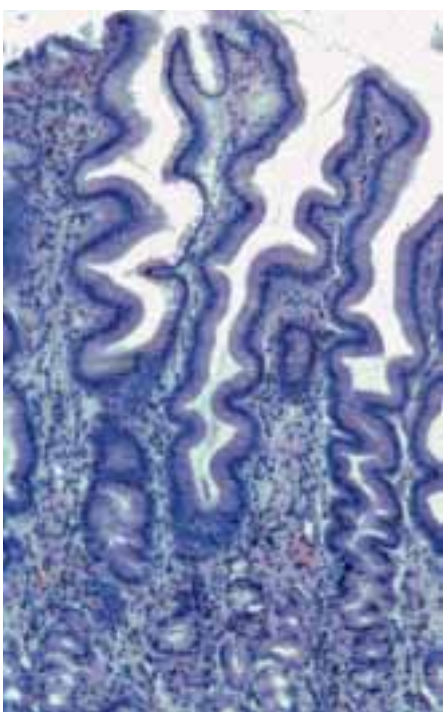

Fig. 3.21 Reactive gastritis with marked foveolar hyperplasia.

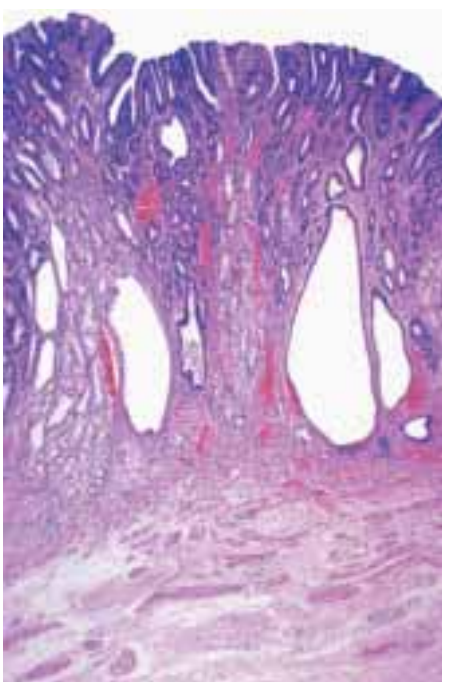

Fig. 3.22 Tubular adenoma of gastric antrum. Uninvolved pyloric glands below the lesion show cystic dilatation.

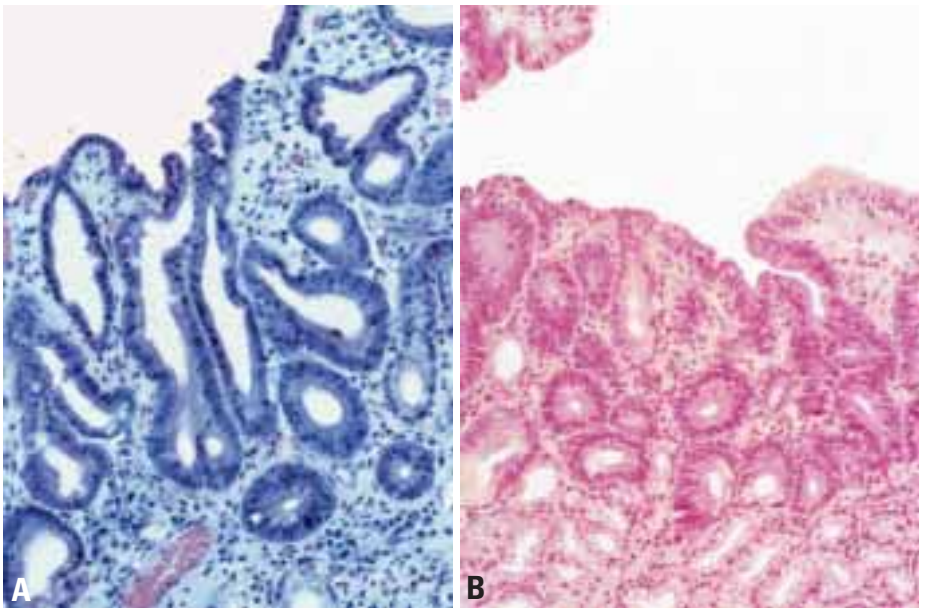

Fig. 3.23 **A, B** Examples of low-grade intraepithelial neoplasia of flat gastric mucosa. The atypia extends to the surface.

ing; there is no stromal invasion. Mucin secretion is absent or minimal. The pleomorphic, hyperchromatic, usually pseudostratified nuclei often are cigar-shaped. Prominent amphophilic nucleoli are common. Increased proliferative activity is present throughout the epithelium.

Progression of intraepithelial neoplasia to carcinoma

Carcinoma is diagnosed when the tumour invades into the lamina propria (intramucosal carcinoma) or through the muscularis mucosae. Some gastric biopsies contain areas suggestive of true invasion (such as isolated cells, gland-like structures, or papillary projections). The term 'suspicious for invasion' is appropriate when the histological criteria for an invasive malignancy are equivocal.

Up to 80% of intraepithelial neoplasias may progress to invasion. Indeed, invasive cancer already may be present in patients found to have high-grade intraepithelial neoplasia with no obvious tumour mass. The extent of intestinal metaplasia associated with intraepithelial neoplasia, together with a sulphomucin-secreting phenotype of the intestinalized mucosa (type III intestinal metaplasia), correlate with an increased risk of carcinoma development.

Adenomas

Adenomas are circumscribed, benign lesions, composed of tubular and/or villous structures showing intraepithelial neoplasia. The frequency of malignant transformation depends on size and histological grade. It occurs in approximately 2% of lesions measuring < 2 cm and in 40-50% of lesions > 2 cm. Flat adenomas may have a greater tendency to progress to carcinoma.

Polyps

Hyperplastic polyps

Hyperplastic polyps are one of the commonest gastric polyps. They are sessile or pedunculated lesions, usually < 2.0 cm in diameter, typically arising in the antrum on a background of *H. pylori* gastritis. They contain a proliferation of surface foveolar cells lining elongated, distorted pits extending deep into the stroma. They may contain pyloric glands, chief cells and parietal cells. The surface often erodes. In a minority of cases, carcinoma develops within the polyps in areas of intestinal metaplasia and dysplasia.

Fundic gland polyps

Fundic gland polyps are the commonest gastric polyp seen in Western populations. They occur sporadically, without a relationship to *H. pylori* gastritis. They also affect patients on long-term proton pump inhibitors or patients with familial adenomatous polyposis (FAP), who may have hundreds of fundic gland polyps {2064, 2065}.

The lesions consist of a localized hyperplasia of the deep epithelial compartment of the oxyntic mucosa, particularly of mucous neck cells, with variable degrees of cystic dilatation. Sporadic fundic gland polyps have no malignant potential. Exceptionally, patients with attentuated FAP may develop dysplasia and carcinoma in their fundic gland polyps {2214, 1204}

Polyposis syndromes

Peutz-Jeghers polyps, juvenile polyps, and Cowden polyps generally do not occur spontaneously, but rather as part of hereditary polyposis syndromes. In the stomach, Peutz-Jeghers polyps are characterized histologically by branching bands of smooth muscle derived from

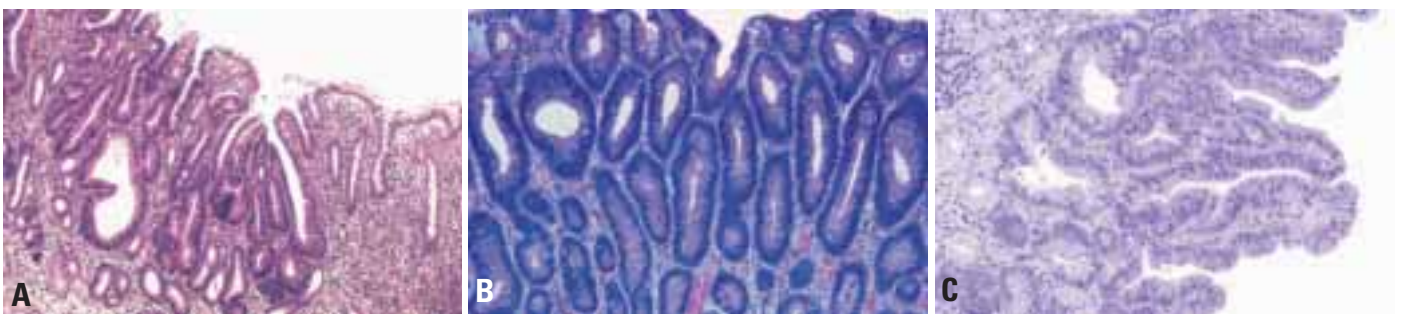

Fig. 3.24 High-grade intraepithelial neoplasia in flat gastric mucosa (flat adenoma). **A** Architectal distortion of the gastric glands. **B** High degree of cellular atypia. **C** Papillary pattern.

Table 3.01
Histological follow-up studies of gastric intraepithelial neoplasia. Proportion progressing to carcinoma and mean interval.

Reports	Low-grade dysplasia			High-grade dysplasia		
Saraga, 1987 {2355}	2%	(1/64)	4 yr.	81%	(17/21)	4 mos.
Lansdown, 1990 {2356}	0	(0/7)		85%	(11/13)	5 mos.
Rugge, 1991 {2008}	17%	(12/69)	1yr.	75%	(6/8)	4 mos.
Fertitta, 1993 {2357}	23%	(7/30)	10 mos.	81%	(25/31)	5 mos.
Di Gregorio, 1993 {2358}	7%	(6/89)	2 yr.	60%	(6/10)	11 mos.
Rugge, 1994 {2009}	14%	(13/90)	2 yr.	78%	(14/18)	9 mos.
Kokkola, 1996 {2359}	0%	(0/96)		67%	(2/3)	1.5 yr.

muscularis mucosae, and hyperplasia, elongation and cystic change of foveolar epithelium; the deeper glandular components tend to show atrophy.

Genetic susceptibility

Most gastric carcinomas occur sporadically; only about 8-10% have an inherited familial component {996}. Familial clustering occurs in 12 to 25% with a dominant inheritance pattern {597, 864}. Case-control studies also suggest a small but consistent increased risk in first-degree relatives of gastric carcinoma patients {2200}.

Gastric carcinoma occasionally develops in families with germline mutations in *ATM5, TP53* (Li Fraumeni syndrome) {2001, 743, 1652}, and *BRCA2* {1934}. Rare site-specific gastric carcinoma predisposition traits have been reported in several families {1147, 2130}, including that of Napoleon.

Hereditary diffuse gastric carcinoma

Germline mutations in the gene encoding the cell adhesion protein E-cadherin *(CDH1)* lead to an autosomal dominant predisposition to gastric carcinoma, referred to as hereditary diffuse gastric carcinoma (HDGC) {640, 568}. Predisposing germline *CDH1* mutations generally resulting in truncated proteins are spread throughout the gene with no apparent hotspots {641, 640, 568, 1581}. HDGC has an age of onset ranging upwards from 14 years and a penetrance of approximately 70% {641, 568}. Histologically, HDGC tumours are diffuse, poorly differentiated infiltrative adenocarcinomas with occasional signet-ring cells {641, 640, 568}.

HNPCC

Gastric carcinomas can develop as part of the hereditary nonpolyposis colon cancer (HNPCC) syndrome {1130, 922}. They are intestinal type cancers, without an association with *H. pylori* infection; most exhibit microsatellite instability (MSI) {4} with a trend that is opposite to that found in tumours arising in young patients {1739}.

Gastrointestional polyposis syndromes

Gastric carcinomas also occur in patients with gastrointestinal polyposis syndromes including FAP and Peutz-Jeghers syndrome.
Overall, gastric carcinoma is rare in these settings, and the exact contribution of the polyposis and underlying germline alterations of *APC* and *LKB1/STK11* to cancer development is unclear.

Blood group A

The blood group A phenotype associates with gastric carcinomas {27, 649}. *H. pylori* adhere to the Lewis^{b} blood group antigen and the latter may be an important host factor facilitating this chronic infection {244} and subsequent cancer risk.

Molecular genetics

Loss of heterozygosity studies and comparative genomic hybridization (CGH) analyses have identified several loci with significant allelic loss, indicating possible tumour suppressor genes important in gastric carcinoma. Common target(s) of loss or gain include chromosomal regions 3p, 4, 5q, (30 to 40% at or near *APC*'s locus) {1656, 1577}, 6q {255}, 9p, 17p (over 60 percent at *TP53*'s locus) {1656}, 18q (over 60 percent at *DCC*'s locus) {1981}, and 20q {1287, 449, 2192}. Similar LOH losses at 11p15 occur in proximal and distal carcinomas, suggesting common paths of develop-

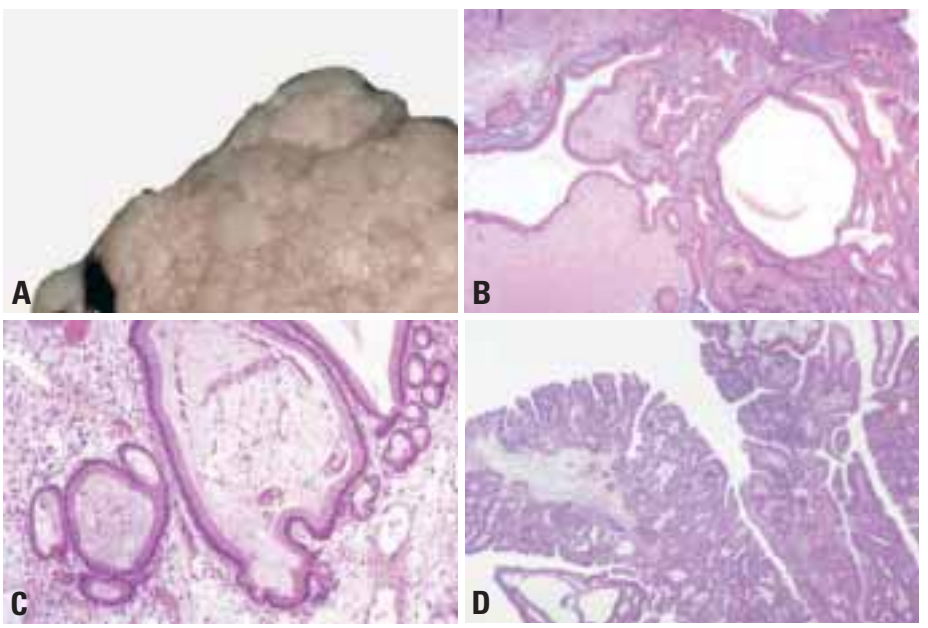

Fig. 3.25 **A** Large hyperplastic polyp of the stomach. **B, C** Typical histology of gastric hyperplastic polyp. **D** Hyperplastic polyp with florid epithelial hyperplasia.

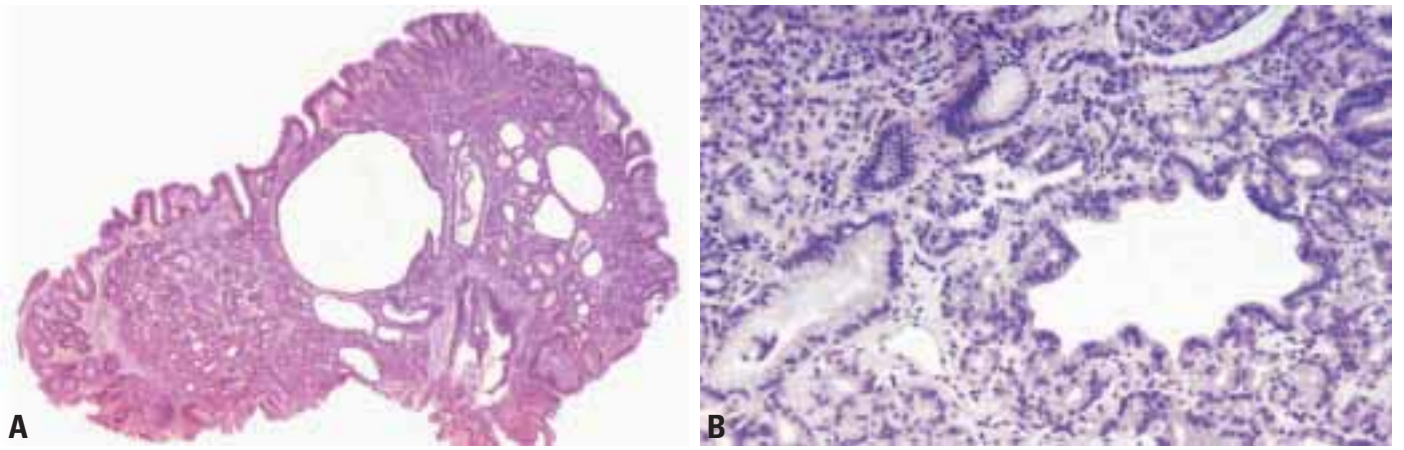

Fig. 3.26 A, B Fundic gland polyp. Cystic glands are typical.

ment {1288}. Loss of a locus on 7q (D7S95) associates with peritoneal metastasis.

The frequency of MSI in sporadic gastric carcinoma ranges from 13% to 44% {1713}. MSI+ tumours tend to be advanced intestinal-type cancers. The degree of genome-wide instability varies with more significant instability (e.g., MSI-H: > 33% abnormal loci) occurring in only 16% of gastric carcinoma, usually of the subcardial intestinal or mixed type, with less frequent lymph node or vessel invasion, prominent lymphoid infiltration, and better prognosis {430}. Loss of either hMLH1 or hMSH2 protein expression affects all MSI-H cases {654} suggesting inactivation of both alleles by mechanisms such as hypermethylation {1050, 510}.

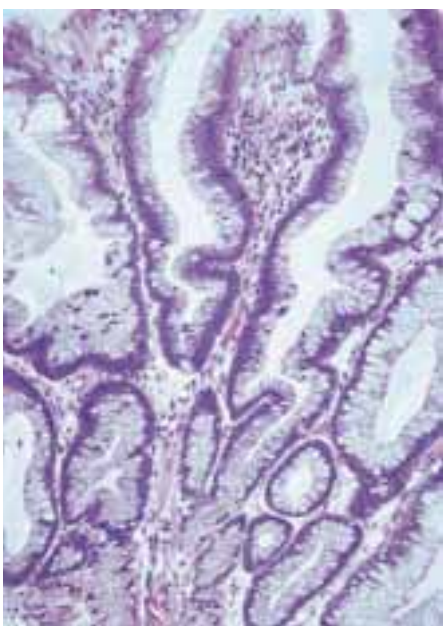

Fig. 3.27 Peutz-Jeghers polyp with hyperplastic glands.

Genes with simple tandem repeat sequences within their coding regions that are altered in MSI+ tumours include the TGF-β II receptor, *BAX, IGFR*II, *hMSH3, hMSH6,* and *E2F-4.* A study of gastric cancers displaying the MSI-H phenotype reveal that a majority contain mutated TGF-β type II receptors in a polyadenine tract {1420, 1462}. Altered TGF-β II receptor genes can also be found in MSI-lesions.

Allelic loss of *TP53* occurs in > 60% of cases and mutations are identified in approximately 30-50% of cases depending on the mutational screening method and sample sizes {729, 1937}. *TP53* mutations are identifiable in some intestinal metaplasias; {497} most alterations affect advanced tumours. *TP53* mutations in gastric lesions resemble those seen in other cancers with a predominance of base transitions, especially at CpG dinucleotides. Immunohistochemical analyses to detect *TP53* overexpression can indirectly identify *TP53* mutations but do not have consistent prognostic value in gastric carcinoma patients {557, 766}. Finally, with respect to *TP53*, there is a polymorphism in codon 72 encoding a proline rather than an arginine that strongly associates with antral cancers {1735}.

Sporadic gastric carcinomas, especially diffuse carcinomas, exhibit reduced or abnormal E-cadherin expression {1196, 1135}, and genetic abnormalities of the E-cadherin gene and its transcripts. Reduced E-cadherin expression is associated with reduced survival {848}. E-cadherin splice site alterations produce exon deletion and skipping. Large deletions including allelic loss and missense point mutations also occur; some tumours exhibit alterations in both alleles {135}. Somatic E-cadherin gene alterations also affect the diffuse component of mixed tumours {1136}. Alpha-catenin, which binds to the intracellular domain of E-cadherin and links it to actin-based cytoskeletal elements, shows reduced immunohistochemical expression in many tumours and correlates with infiltrative growth and poor differentiation {1189}. Beta catenin may also be abnormal in gastric carcinoma.

There is evidence of a tumour suppressor locus on chromosome 3p in gastric carcinomas {893, 1688}. This area encodes the *FHIT* gene. Gastric carcinomas develop abnormal transcripts, deleted exons {1411}, a somatic missense mutation in exon 6 and loss of FHIT protein expression {102}.

Somatic *APC* mutations, mostly missense in nature and low in frequency, affect Japanese patients with in situ and invasive neoplasia {1309}. Significant allelic loss (30%) at the *APC* loci suggest that there is a tumour suppressor gene important in gastric tumourigenesis nearby. Indeed, alternative loci have been mapped to commonly deleted regions in gastric carcinomas {1891}.

Amplification and overexpression of the *c-met* gene encoding a tyrosine kinase receptor for the hepatocyte growth factor occurs in gastric carcinoma {976}. Other growth factor and receptor signal systems that may be involved include epidermal growth factor, TGF-alpha, interleukin-1-a, cripto, amphiregulin, platelet-derived

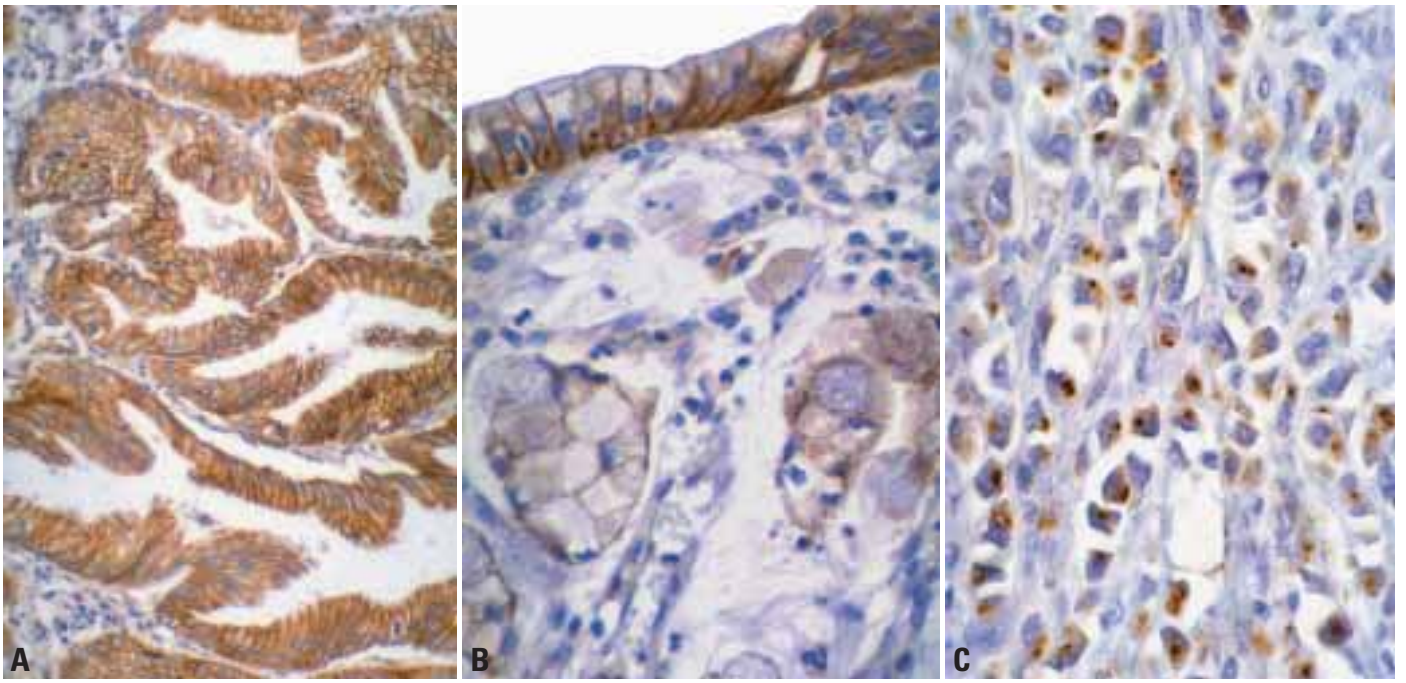

Fig. 3.28 E-cadherin expression in gastric adenocarcinoma. **A** Intestinal type of adenocarcinoma showing a normal pattern of membranous staining. **B** Diffuse type of adenocarcinoma with reduced E-cadherin expression. Normal expression can be seen in the non-neoplastic gastric epithelium overlying the tumour. **C** Undifferentiated gastric carcinoma with highly reduced membranous expression and dot-like cytoplasmic expression.

growth factor, and K-sam {1879}. Amplification of *c-erbB-2,* a transmembrane tyrosine kinase receptor oncogene, occurs in approximately 10% of lesions and overexpression associates with a poor prognosis {375}. Telomerase activity has been detected by a PCR-based assay frequently in the late stages of gastric tumours and observed to be associated with a poor prognosis {719}.

Prognosis and predictive factors

Early gastric cancer

In early gastric cancers, small mucosal (< 4 cm), superficial (> 4 cm) and Pen B lesions have a low incidence of vessel invasion and lymph node metastasis and a good prognosis after surgery (about 90% of patients survive 10 years). In contrast, penetrating lesions of the Pen A type are characterized by a relatively high incidence of vessel invasion and lymph node metastasis and a poor prognosis after surgery (64.8% 5-year survival).

Advanced gastric cancer

Staging. The TNM staging system for gastric cancer is widely used and it provides important prognostic information. Lymphatic and vascular invasion carries a poor prognosis and is often seen in advanced cases. Lymph node status, which is part of the TNM system, is also an important prognostic indicator. The 5th edition of the UICC TNM Classification of Malignant Tumours {66} and the AJCC Manual for the Staging of Cancer {1} published in 1997, have a number-based classification scheme for reporting nodal involvement in gastric cancer.

Roder et al recently published data supporting the value of this reporting system. These authors found that for patients who had nodal involvement in 1-6 lymph nodes (pN1), the 5-year sur-

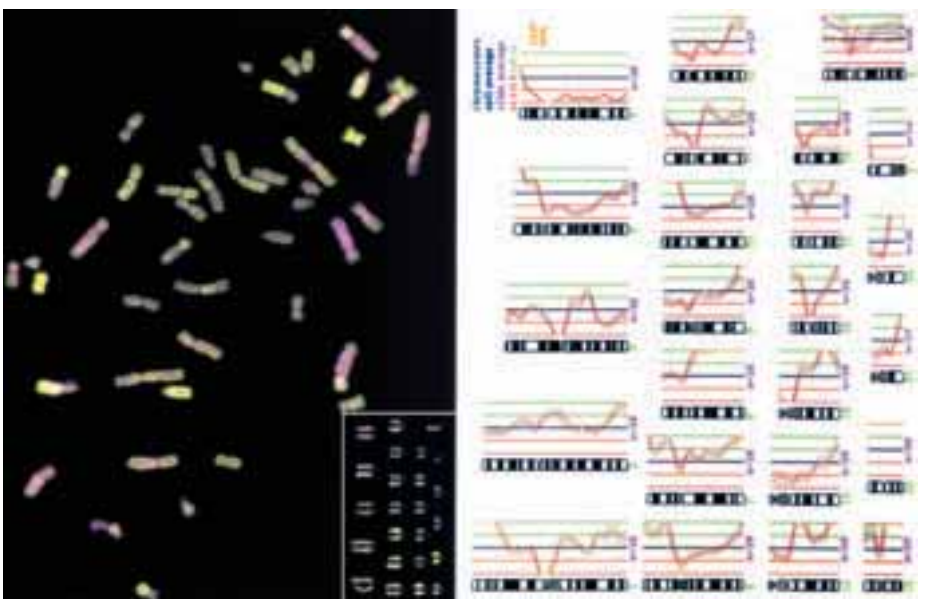

Fig. 3.29 CGH analysis of a poorly differentiated gastric adenocarcinoma: copy number gains at chromosomes 3q21, 7p15, 8q, 10p12-15, 11q13, 12q24, 13q13-14, 15q23-25, 17q24, 20 and 21q21. Copy number losses at chromosomes 4q12-28 and 5.

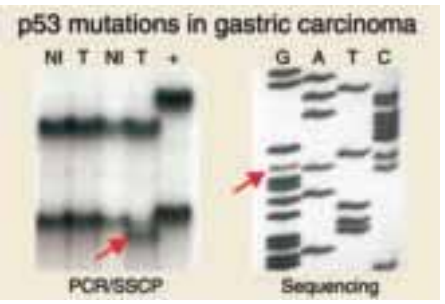

Fig. 3.30 *TP53* mutations in gastric carcinoma. The mutations are shown by both single-strand conformation polymorphisms (SSCP) as well as direct sequencing. There is a G to A substitution indicated by the right hand panel.

vival rate was 44% compared with a 30% survival rate in patients with 7-15 lymph nodes involved with tumour (pN2). Patients with more than 15 lymph nodes involved by metastatic tumour (pN3) had an even worse 5-year survival of 11% {1602}. Gastric carcinoma with obvious invasion beyond the pyloric ring, those with invasion up to the pyloric ring, and those without evidence of duodenal invasion have 5-year survival rates of 8%, 22%, and 58%, respectively {671}. Patients with T1 cancers limited to the mucosa and submucosa have a 5-year survival of approximately 95%. Tumours that invade the muscularis propria have a 60-80% 5-year survival, whereas tumours invading the subserosa have a 50% 5-year survival {2181}. Unfortunately, most patients with advanced carcinoma already have lymph node metastases at the time of diagnosis.

Histological features. The value of the histological type of tumour in predicting tumour prognosis is more controversial. This relates in part to the classification scheme that is used to diagnose the cancers. Using the Laurén classification, some believe that diffuse lesions generally carry a worse prognosis than intestinal carcinomas. The prognosis is particularly bad in children and young adults, in whom the diagnosis is often delayed {1986, 1554} and likely fit into the category of HDGC. However, others have not found the Laurén classification to predict prognosis {1788, 1177}. One study found that only the Goseki classification {610} added additional prognostic information to the TNM stage {610}. 5-year survival of patients with mucus rich (Goseki II and IV) T3 tumours was significantly worse than that of patients with mucus poor (Goseki I and III) T3 tumours (18% vs. 53% $p<0.003$) {1177}. A second study validated these findings {1788}. Another classification scheme for gastric carcinoma was proposed by Carneiro et al that may also have prognostic value {610}.

The recognition of mixed carcinoma may be important since patients harbouring this type of carcinoma may also have a poor outcome {610}.

Some patients with medullary carcinomas with circumscribed, pushing growth margins and a marked stromal inflammatory reaction exhibit a better prognosis than those with other histological tumour types {430}. Some of these patients are in HNPCC kindreds who have MSI-H, a feature associated with better survival. However, not all studies agree that stromal response and pushing margins predict a better prognosis {1788, 1177}.

In summary, gastric carcinoma is a heterogeneous disease biologically and genetically, and a clear working model of gastric tumourigenesis has yet to be formulated. More tumours appear to be related to environmental than to genetic causes, although both may play a role in individual cases. Characterization of the various pathways should afford multiple opportunities to design more specific and therefore more effective therapies.

Endocrine tumours of the stomach

C. Capella
E. Solcia
L.H. Sobin
R. Arnold

Definition

Most endocrine tumours of the stomach are well differentiated, nonfunctioning enterochromaffin-like (ECL) cell carcinoids arising from oxyntic mucosa in the corpus or fundus. Three distinct types have are recognized: (1) Type I, associated with autoimmune chronic atrophic gastritis (A-CAG); (2) type II, associated with muliple endocrine neoplasia type 1 (MEN-1) and Zollinger-Ellison syndrome (ZES); type III, sporadic, i.e. not associated with hypergastrinaemia or A-CAG.

ICD-O Code

Carcinoid	8240/3
Small cell carcinoma	8041/3

Epidemiology

In the past, carcinoid tumours of the stomach have been reported to occur with an incidence of 0.002-0.1 per 100,000 population per year and to account for 2-3 % of all gastrointestinal carcinoids {587} and 0.3 percent of gastric neoplasms {1132}. More recent studies, however, based on endoscopic techniques and increased awareness of such lesions, have shown a much higher incidence of gastric carcinoids, which may now account for 11-41% of all gastrointestinal carcinoids {1588, 1764, 1782}. The incidence of gastric carcinoids is higher in Japan, where they re-present 30% of all gastrointestinal carcinoids, which may be due to the high incidence of chronic atrophic gastritis in this country {1277}.

Age and sex distribution

Type I gastric ECL-cell carcinoids have been reported to represent 74% of gastric endocrine tumours and to occur most often in females (M:F ratio, 1:2.5). The mean age at biopsy is 63 years (range 15-88 years). Type II ECL-cell carcinoids represent 6% of all gastric endocrine tumours and show no gender predilection (M:F ratio, 1:1) at a mean age of 50 years (range 28-67 years) {1590}. Type III ECL-cell carcinoids constitute 13% of all gastric endocrine tumours and are observed mainly in male patients (M:F ratio, 2.8:1) at a mean age of 55 years (range 21-38 years) {1590}.

Small cell carcinoma (poorly differentiated endocrine carcinoma) accounts for 6% of gastric endocrine tumours and prevails in men (M:F ratio, 2:1) at a mean age of 63 years (range 41-61 years) {1590}. Gastrin cell tumours represent less than 1% of gastric endocrine tumours {1590} and are reported in adults (age range 55-77).

Aetiology

Gastrin has a trophic effect on ECL-cells both in humans and experimental animals {172, 652}. Hypergastrinaemic states, resulting either from unregulated hormone release by a gastrinoma or from a secondary response of antral G cells to achlorhydria, are consistently associated with ECL-cell hyperplasia {172}.

Autoimmune chronic atrophic gastritis (A-CAG)

This disease is caused by antibodies to parietal cells of the oxyntic mucosa. It leads to chronic atrophic gastritis (with or without pernicious anaemia) which leads to an increase in gastrin production.

Zollinger-Ellison syndrome

This disease results from hypergastrinaemia due to gastrin-producing neoplasms that are preferentially located in the small intestine and pancreas. ECL-cell proliferation is usually limited to hyperplastic lesions of the simple linear type {1042, 1777}.

MEN-1

This inherited tumour syndrome causes a variety of endocrine neoplasms, including gastrinomas. In patients with MEN-1 associated ZES (MEN-1/ZES), ECL-cell lesions are usually dysplastic or overtly carcinoid in nature {1779}. In the MEN-1 syndrome, the mutation or deletion of the suppressor MEN-1 oncogene in 11q13 may be involved {394} as an additional pathogenetic factor. In A-CAG, achlorhydria or associated mucosal changes may contribute to tumourigenesis {1785}. Several growth factors, including transforming growth factor-α (TGFα) and basic fibroblast growth factor (bFGF) seem to be involved in tumour development and progression as well as stromal and vascular proliferation of ECL-cell carcinoids {171}.

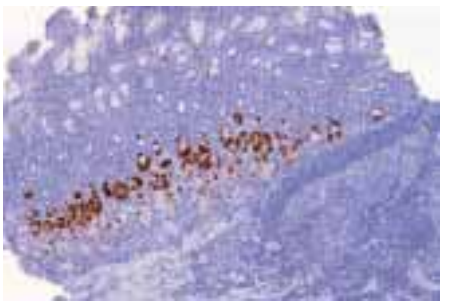

Fig. 3.31 Chromogranin A immunostain demonstrates hyperplasia of endocrine cells at the base of glandular tubules.

Localization

Type I, II, and III ECL-cell carcinoids are all located in the mucosa of the body-fundus of the stomach, whereas the rare G-cell tumours are located in the antro-pyloric region. Small cell carcinomas prevail in the body/fundus, but some are located in the antrum {1590}.

Clinical features

The three distinct types of ECL-cell carcinoids are well differentiated growths but with variable and poorly predictable behaviour.

Type I ECL-cell carcinoids

These are associated with A-CAG involving the corpus and fundus mucosa. Clinical signs include achlorhydria and, less frequently, pernicious anemia. Hypergastrinaemia or evidence of antral gastrin-cell hyperplasia is observed in all cases of A-CAG. In patients with a carcinoid, ECL-cell hyperplastic changes are a constant feature and dysplastic growths are frequently observed {1590}. A-CAG associated carcinoids are typically small (usually less than 1 cm), mul-

tiple and multicentric. Of 152 cases studied by endoscopy, 57% had more than two growths {1561}.

Type II ECL-cell carcinoids
Hypertrophic, hypersecretory gastropathy and high levels of circulating gastrin are critical diagnostic findings. In all cases, ECL-cell hyperplasia and/or dysplasia were noted in the fundic peritumoural mucosa {1590}. These gastric carcinoids are usually multiple and smaller than 1.5 cm in size in the majority of cases {1590}.

Type III (sporadic) ECL-cell carcinoids
These lesions are not associated with hypergastinaemia or A-CAG. They are generally solitary growths, and arise in the setting of gastric mucosa devoid of ECL-cell hyperplasia/dysplasia and of significant pathologic lesions except for gastritis (other than A-CAG). Rare multiple tumours have been observed {1590}. Clinically, type III tumours present (1) as a mass lesion with no evidence of endocrine symptoms (nonfunctioning carcinoid) and with clinical findings similar to those of adenocarcinoma, including gastric haemorrhage, obstruction and metastasis, or (2) with endocrine symptoms of an 'atypical carcinoid syndrome' with red cutaneous flushing and absence of diarrhoea, usually coupled with liver metastases and production of histamine and 5-hydroxytryptophan {1386, 1598}.

Non ECL-cell gastric carcinoids.
These uncommon tumours may present with ZES due to their gastrin production (which is more frequently found in duodenal gastrinomas) or with Cushing syndrome due to secretion of adrenocorticotrophic hormone (ACTH) {711, 1791}.

Macroscopy
Type I ECL-cell carcinoids are multiple in 57% of cases {1590}, usually appearing as small tan nodules or polyps that are circumscribed in the mucosa or, more often, to the submucosa. Most tumours (77%) are < 1 cm in maximum diameter and 97% of tumours are < 1.5 cm. The muscularis propria is involved in only a minority of cases (7%) {1590}.
The stomachs with type II tumours are enlarged and show a thickened gastric wall (0.6-4.5 cm) due to severe hypertrophic-hypersecretory gastropathy and multiple mucosal-submucosal nodules which, though larger than those of type I, are generally smaller than 1.5 cm in size in 75% of cases {1590}.
Type III ECL-cell tumours are usually single and in 33% of the cases larger than 2 cm in diameter. Infiltration of the muscularis propria is found in 76%, and of the serosa in 53% of cases {1590}.

Histopathology
The histopathological categorization of endocrine tumours of the stomach described here, is a modification of the WHO classification of endocrine tumours {1784}.

Carcinoid tumour
A carcinoid is defined morphologically as a well differentiated neoplasm of the diffuse endocrine system.

ECL-cell carcinoid
The majority of type I and type II ECL-cell carcinoids are characterized by small, microlobular-trabecular aggregates formed by regularly distributed, often aligned cells (mosaic-like pattern), with regular, monomorphic nuclei, usually inapparent nucleoli, rather abundant, fairly eosinophilic cytoplasm, almost absent mitoses, and infrequent angioinvasion.
Tumours with these features (grade 1 according to Rindi et al {1589}) are generally limited to mucosa or submucosa {1589} and can be considered as tumours with benign behaviour. The ECL nature of the tumours is confirmed by strong argyrophilia by Grimelius or Sevier Munger techniques and positive immunoreactivity for chromogranin A, in the absence of reactivity for the argentaffin or diazonium tests for serotonin, and no or only occasional immunoreactivity for hormonal products {1591}. Minor cell sub-populations expressing serotonin, gastrin, somatostatin, pancreatic polypeptide (PP), or α-hCG have been detected in a minority of tumours {1591}. A few ECL-cell tumours produce histamine and 5-hydroxy-tryptophan; these lesions, when they metastasize, can produce 'atypical' carcinoid syndrome {1591}
Vesicular monoamine transporter type 2 (VMAT-2) is a suitable and specific marker for ECL-cell tumours {1592} while histamine or histidine decarboxylase immunohistochemical analysis, although specific, is less suitable for routinely processed

Fig. 3.32 Sporadic (type III) ECL-cell carcinoid of the gastric body. The surrounding mucosa is normal.

specimens {1865}. The ECL-cell nature of argyrophil tumours is ultimately assessed by demonstrating ECL-type granules by electron microscopy {232, 1591}.
Sporadic ECL-cell carcinoids are usually more aggressive than those associated with A-CAG or MEN-1. Histopathologically, these tumours show a prevalence of solid cellular aggregates and large trabeculae, crowding, and irregular distribution of round to spindle and polyhedral tumour cells, fairly large vesicular nuclei with prominent eosinophilic nucleoli, or smaller, hyperchromatic nuclei with irregular chromatin clumps and small nucleoli, considerable mitotic activity, sometimes with atypical mitotic figures and scarce necrosis.
Tumours with these histological features or grade 2 features {1589} show a higher mitotic rate (mean of 9 per 10 HPF), a frequent expression of p53 (60%), a higher

Table 3.02.
Histological classification of endocrine neoplasms of the stomach[1]

1. Carcinoid –
well differentiated endocrine neoplasm
1.1 ECL-cell carcinoid
1.2 EC-cell, serotonin-producing carcinoid
1.3 G-cell, gastrin-producing tumour
1.4 Others
2. Small cell carcinoma –
poorly differentiated endocrine neoplasm
3. Tumour-like lesions
Hyperplasia
Dysplasia

[1] Benign behaviour of ECL-cell carcinoid is associated with the following: tumour confined to mucosa-submucosa, nonangioinvasive, < 1cm in size, nonfunctioning; occurring in CAG or MEN-1/ ZES. Aggressive behaviour of ECL-cell carcinoid is associated with the following: tumour invades muscularis propria or beyond, > 1cm in size, angioinvasive, functioning, and sporadic occurrence.

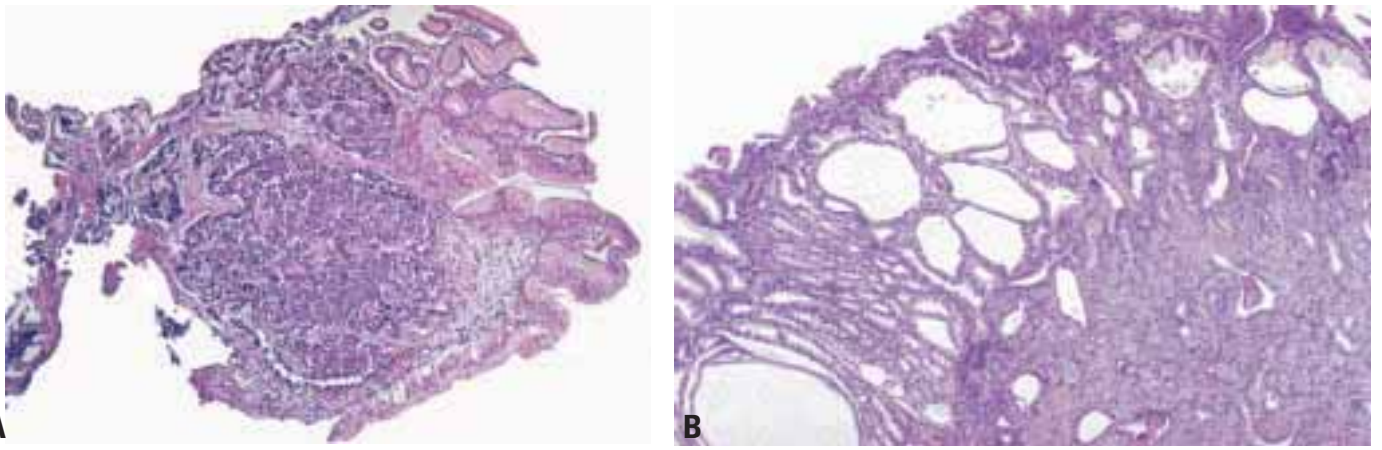

Fig. 3.33 **A** Type I ECL-cell carcinoid in a patient with pernicious anaemia. **B** Type II ECL-cell carcinoid in a patient with MEN1 and ZES.

Ki67 labelling index (above 1000 per 10 HPF) and more frequent lymphatic and vascular invasion than well differentiated ECL-cell carcinoids {1589}. In addition, deeply invasive tumours are associated with local and/or distant metastases in most cases.

EC-cell, serotonin-producing carcinoid
This is a very rare tumour in the stomach {1591}. It is formed by rounded nests of closely packed small tumour cells, often with peripheral palisading, reminiscent of the typical type A histologic pattern of the argentaffin EC-cell carcinoid of the midgut. The tumour cells are argentaffin, intensely argyrophilic and reactive with chromogranin A and anti-serotonin antibodies. Electron microscopic examination confirms the EC-cell nature by detecting characteristic pleomorphic, intensely osmiophilic granules similar to those of normal gastric EC-cells.

Gastrin-cell tumours
Most well differentiated gastrin-cell tumours are small mucosal-submucosal nodules, found incidentally at endoscopy or in a gastrectomy specimen. They may show a characteristic thin trabecular-gyriform pattern or a solid nest pattern. The cells are uniform with scanty cytoplasm and show predominant immunoreactivity for gastrin.

Small cell carcinoma (poorly differentiated endocrine neoplasm)
These are identical to small cell carcinomas of the lung. They correspond to grade 3 tumours according to Rindi et al. {1589}, and are particularly aggressive, malignant tumours {1591}.

Large cell neuroendocrine carcinoma is a malignant neoplasm composed of large cells having organoid, nesting, trabecular, rosette-like and palisading patterns that suggest endocrine differentiation, and in which the last can be confirmed by immunohistochemistry and electron microscopy. In contrast to small cell carcinoma, cytoplasm is more abundant, nuclei are more vesicular and nucleoli are prominent {1954}. These tumours have not been well described in the gastrointestinal tract because of their apparent low frequency {1188}.

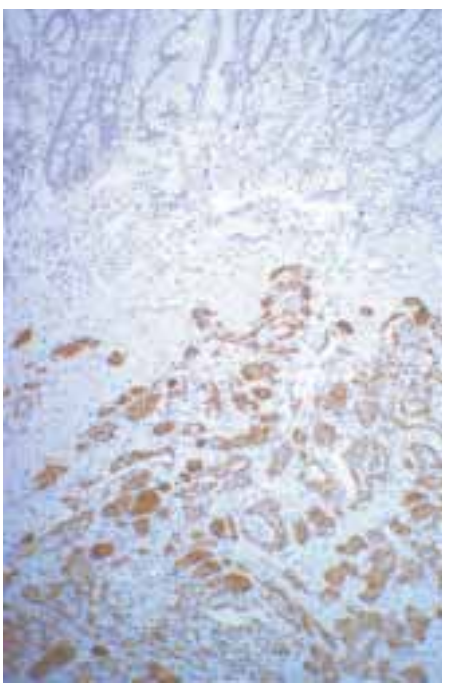

Fig. 3.34 ECL-cell carcinoid showing immunoexpression of chromogranin A.

Mixed exocrine-endocrine carcinomas
These consist of neoplastic endocrine cells composing more than 30% of the whole tumour cell population. They are relatively rare in the stomach, despite the frequent occurrence of minor endocrine components inside the ordinary adenocarcinoma. They should generally be classified as adenocarcinomas.

Precursor lesions
ECL-cell carcinoids arising in hypergastrinaemic conditions (types I and II) develop through a sequence of hyperplasia-dysplasia-neoplasia that has been well documented in histopathological studies {1777}. The successive stages of hyperplasia are termed simple, linear, micronodular, and adenomatoid. Dysplasia is characterized by relatively atypical cells with features of enlarging or fusing micronodules, micro-invasion or newly formed stroma. When the nodules increase in size to > 0.5 mm or invade into the submucosa, the lesion is classified as a carcinoid. The entire spectrum of ECL-cell growth, from hyperplasia to dysplasia and neoplasia has been observed in MEN-1/ZES and autoimmune chronic atrophic gastritis (A-CAG). A similar sequence of lesions has been shown in experimental models of the disease, mostly based on hypergastrinaemia secondary to pharmacological inhibition of acid secretion in rodents {1896}.

Genetic susceptibility
ECL-cell carcinoids are integral components of the MEN-1 syndrome {1042}. In patients with familial MEN-1/ZES, type II gastric carcinoids arise in 13-30% of cases {854, 1042}. However, patients

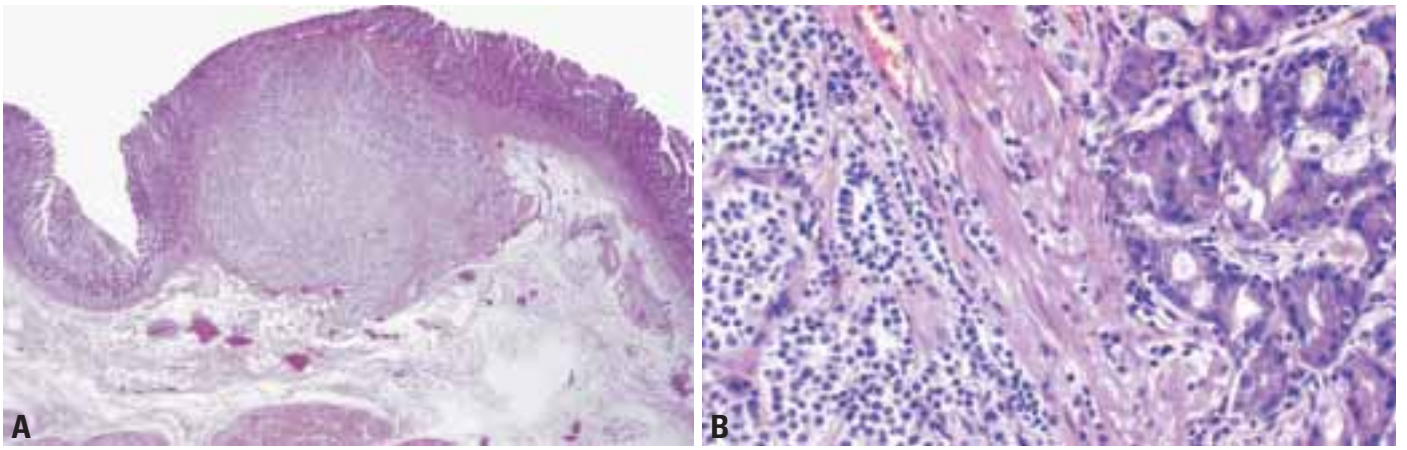

Fig. 3.35 Sporadic (type III) ECL carcinoid. **A** Tumour extends from mucosa into submucosa with well delineated inferior border. **B** The carcinoid (left) has round, regular, isomorphic nuclei.

with sporadic ZES rarely develop gastric carcinoids despite serum gastrin levels, which persist 10 fold above normal for a prolonged time.

Diagnostic criteria of MEN-1

This rare dominantly inherited disorder is characterized by the synchronous or metachronous development of multiple endocrine tumours in different endocrine organs by the third decade of life. The parathyroid glands are involved in 90-97%, endocrine pancreas in 30-82%, duodenal gastrinomas in 25%, pituitary adenomas in more than 60%, and foregut carcinoids (stomach, lung, thymus) in 5-9% of cases {394}. Other, so-called non-classical MEN-1 tumours, such as cutaneous and visceral lipomas, thyroid and adrenal adenomas, and skin angiofibromas, may occur {394, 1444}.

MEN-1 gene

MEN-1 has been mapped to chromosome 11q13 {107, 1015}. It encodes for a 610 amino acid nuclear protein, termed 'menin', whose suppressor function involves direct binding to JunD and inhibition of JunD activated transcription {271, 18}. The tumour suppressor function of the gene has been proposed based on the results of combined tumour deletion and pedigree analysis {107, 271, 394}. High rates of loss of heterozygosity (LOH) at the *MEN-1* gene locus have been reported in classic tumours of the MEN-1, such as endocrine pancreatic, pituitary and parathyroid neoplasms {1553, 1923}. LOH at 11q13 of type II gastric carcinoids was found in 9 of 10 MEN-1 patients investigated {123, 173, 219, 394}.

These findings support the concept that these gastric tumours are integral components of the MEN-1 phenotype, sharing with parathyroid and islet cell tumours the highest frequency of LOH at 11q13. In multiple carcinoids from the same stomach, the deletion size in the wild-type allele differed from one tumour to another, suggesting a multiclonal origin {394}. One of the type II tumours showing LOH at 11q13 was in a patient who had neither ZES nor hypergastrinaemia {173}, suggesting that inactivation of the *MEN-1* gene alone is capable of causing ECL-cell tumours without requiring the promoting effect of hypergastrinaemia.

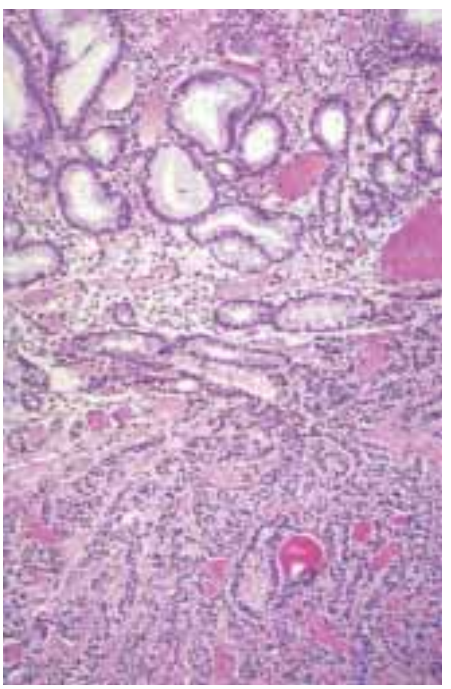

Fig. 3.36 Gastrin cell tumour (gastrinoma) of the pylorus with trabecular growth pattern.

The role of *MEN-1* in non MEN-associated gastric carcinoids is more controversial. Analysing six type I gastric carcinoids, Debelenko et al. {394} found 11q13 LOH in one tumour while D'Adda et al. {363} detected 11q13 LOH in 12 out of 25 cases (48%). Large deletions in both the 11q13 and 11q14 regions were observed in two poorly differentiated endocrine carcinomas {363}.

Prognosis and predictive factors

The prognosis of carcinoids is highly variable, ranging from slowly growing benign lesions to malignant tumours with extensive metastatic spread.

Benign behaviour of ECL-cell carcinoids is associated with the following: tumour confined to mucosa-submucosa, nonangioinvasive, < 1 cm in size, nonfunctioning; occurring in CAG or MEN-1/ ZES. Type I, A-CAG associated tumours, have an excellent prognosis, as do most type II MEN-1/ZES tumours.

Aggressive behaviour of ECL-cell carcinoid is associated with the following: tumour invades muscularis propria or beyond, is > 1 cm in size, angioinvasive, functioning, with high mitotic activity and sporadic occurrence {1591, 1590, 1589}.

Metastasis. Lymph node metastases are detected in 5% of type I and 30% of type II cases, while distant (liver) metastases are found respectively in 2.5% and 10% of cases. No tumour-related or only exceptional death was observed among patients with type I carcinoid, while only 1/10 patients died of type II carcinoid. On

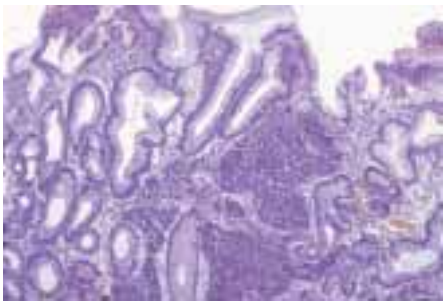

Fig. 3.37 Small cell carcinoma of the stomach.

the other hand, lymph node metastases are found in 71% and distant metastases in 69% of patients with type III tumours; death from the tumour occurs in 27% of patients with a mean survival of 28 months {1590}.

Therapy

Polypoid type I carcinoids < 1cm, fewer than 3-5 in number, associated with A-CAG can be endoscopically excised and have an excellent prognosis. If larger than 1 cm or more than 3-5 lesions are present, antrectomy and local excision of all accessible fundic lesions is recommended.

In type II carcinoids the clinical evolution depends on the behaviour of associated pancreatic and duodenal gastrinomas more than on the behaviour of gastric tumours, although some aggressive ECL-cell carcinomas may be fatal {173}. In such patients, careful search for associated pancreatic, duodenal, parathyroid, or other tumours and family investigation for the MEN-1 gene mutation are needed. Type III (sporadic) ECL-cell carcinoids > 1 cm generally require surgical resection even when they are histologically well differentiated.

Lymphoma of the stomach

A. Wotherspoon
A. Chott
R.D. Gascoyne
H.K. Müller-Hermelink

Definition

Primary gastric lymphomas are defined as lymphomas originating from the stomach and contiguous lymph nodes. Lymphomas at this site are considered primary if the main bulk of disease is located in the stomach. The majority of gastric lymphomas are high-grade B-cell lymphomas, some of which have developed through progression from low-grade lymphomas of mucosa associated lymphoid tissue (MALT). The low-grade lesions are almost exclusively B-cell MALT lymphomas.

Historical annotation

Classically, primary gastric lymphomas have been considered to be lymphomas that are confined to the stomach and the contiguous lymph nodes {378}. While this excludes cases of secondary involvement of the stomach by nodal-type lymphomas – which may occur in up to 25% of nodal lymphomas {508} – this definition is excessively restrictive and excludes more disseminated, higher stage lymphomas arising within the stomach as well as those with bone marrow involvement. Today, stomach lymphomas are considered primary if the main bulk of disease is present in the stomach. Recognition of morphological features characteristic of primary extranodal lymphomas of mucosa-associated lymphoid tissue-type helps in defining these lesions as primary to the stomach irrespective of the degree of dissemination.

Epidemiology

Approximately 40% of all non-Hodgkin lymphomas arise at extranodal sites {1438, 527}, with the gastrointestinal tract as the commonest extranodal site, accounting for about 4-18% of all non-Hodgkin lymphomas in Western countries and up to 25% of cases in the Middle East. Within the gastrointestinal tract, the stomach is the most frequent site of involvement in Western countries while the small intestine is most frequently affected in Middle Eastern countries. Lymphoma constitutes up to 10% of all gastric malignancies; its incidence appears to be increasing but this may, at least in part, be due to the recognition of the neoplastic nature of lesions previously termed 'pseudolymphoma' {677}.

Gastric lymphoma has a worldwide distribution; somewhat higher incidences have been reported for some Western communities with a high prevalence of *Helicobacter pylori* infection {420}. Primary Hodgkin disease is very rare in the gastrointestinal tract.

Age and sex distribution

Incidence rates are similar in men and women. The age range is wide but the majority of patients are over 50 years at presentation.

Aetiology

Helicobacter pylori infection

Initial studies of low-grade MALT lymphoma suggested that the tumour was associated with *H. pylori* in 92-98% of cases {447, 2135}; subsequent studies have suggested an association in 62-77% {1316, 583, 2146, 890, 178}. *H. pylori* infection is seen less frequently in high-grade lymphomas with a low-grade component (52-71%) and in pure high-grade lymphomas (25-38%) {583,

890, 178}. The organism has been shown to be present in 90% of cases limited to the mucosa and submucosa, falling to 76% when deep submucosa is involved, and is present in only 48% of cases with extension beyond the submucosa {1316}. It has been shown that the infection by *H. pylori* precedes the development of lymphoma, both by sequential serological studies {1474} and by retrospective studies of archival gastric biopsy material {2211, 1314}.

There is some controversy surrounding the role of the organism's genetic features and the risk of lymphoma development. Studies of the association between MALT lymphoma and cagA bearing *H. pylori* strains have produced conflicting results, ranging from a lack of association between cagA and lymphoma {1492, 384} to a strong association {441}. One study claimed no association with low-grade lymphoma but a high frequency of cagA strains in high-grade lesions {1492}. Recently, a truncated form of an *H. pylori* associated protein, fldA, has been shown to be closely associated with gastric MALT lymphoma. All strains of *H. pylori* associated with MALT lymphoma showed a nucleotide G insertion at position 481 of the *fldA* gene, compared to 6/17 stains unassociated with lymphoma. This mutation causes a short truncation in the protein and antibodies to this truncated protein could be detected in 70% of the patients studied with MALT lymphoma, compared to 17% of control patients {274}.

Immunosuppression

Lymphomas may arise or involve the stomach in patients with both congenital and acquired immunodeficiencies. In general, the incidence, clinical features and the histology of the lesions is indistinguishable from those that develop outside the stomach. Up to 23% of gastrointestinal tract non-Hodgkin lymphomas arising in HIV infected patients occur in the stomach and the vast majority of these are large B-cell or Burkitt/Burkitt-like lymphomas, {122} although occasional low-grade MALT lymphomas are described {2132}.

Clinical features

Symptoms and signs

Patients with low-grade lymphomas often present with a long history of non-specific symptoms, including dyspepsia, nausea and vomiting. High-grade lesions may appear as a palpable mass in the epigastrium and can cause severe symptoms, including weight loss.

Imaging

Low-grade MALT lymphomas present as intragastric nodularity with preferential location in the antrum {2180}. A more precise assessment is obtained with spiral CT, particularly if this is used in conjunction with distension of the stomach by water. This technique can identify up to 88% of cases, most of which have nodularity or enlarged rugal folds, and it can assess the submucosal extent of the tumour {1493}. High-grade lymphomas are usually larger and more frequently associated with the presence of a mass and with ulceration. In some cases, the radiological features may mimic diffuse adenocarcinoma {1059}. Endoscopic ultrasound is emerging as the investigation of choice in the assessment of the extent of lymphoma infiltration through the gastric wall. Local lymph node involvement can also be assessed by this technique.

Endoscopy

Some cases show enlarged gastric folds, gastritis, superficial erosions or ulceration. In these cases the surrounding normal appearing gastric mucosa may harbour lymphoma, and accurate mapping of the lesion requires multiple biopsies from all sites including areas appearing macroscopically normal. In a proportion of cases, endoscopic examination shows very minor changes such as hyperaemia and in a few cases random biopsies of apparently entirely normal mucosa may reveal lymphoma. High-grade lymphoma is usually associated with more florid lesions, ulcers and masses. It is often impossible to distinguish lymphoma from carcinoma endoscopically.

MALT lymphomas

Pathogenesis

The normal gastric mucosa contains scattered lymphocytes and plasma cells but is devoid of organised lymphoid tissue. The initial step in the development of primary gastric lymphoma is the acquisition of organised lymphoid tissue from within which the lymphoma can develop. In most cases, this is associated with infection by *H. pylori* {572}, although it has also been seen following infection by

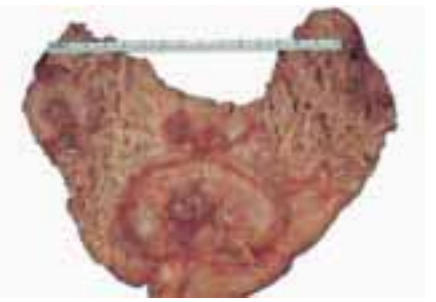

Fig. 3.38 Multifocal malignant lymphoma of the stomach. The two larger lesions are centrally ulcerated.

Helicobacter heilmannii {1842} and in association with coeliac disease {227}. This organised lymphoid tissue shows all the features of MALT, including the infiltration of the epithelium by B-lymphocytes reminiscent of the lymphoepithelium seen in Peyer patches {2135}.

The cellular basis of the interaction between *H. pylori* and MALT lymphoma cells has been studied in detail. When unseparated cells isolated from low-grade gastric MALT lymphomas are incubated in vitro with heat treated whole cell preparations from *H. pylori*, the tumour cells proliferate while those cultured in the absence of the organism or stimulating chemical mitogen rapidly die {768}. The proliferative response appeared to be strain specific for individual tumours but varied between tumours from different patients {768}. When T-cells were removed from the culture system the proliferative response was not seen and this could not be induced if the T-cells were replaced by supernatant from other cultures containing unseparated tumour derived cells {769}. Together these studies show that the proliferation of the MALT lymphoma is driven by the presence of the *H. pylori* but that this, rather than being a direct effect on the tumour

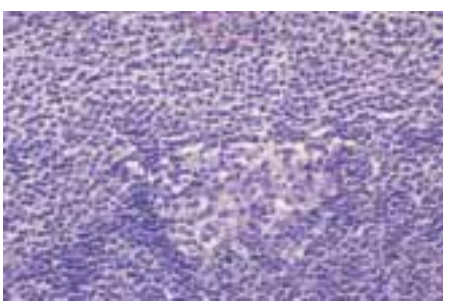

Fig. 3.39 Low-grade B-cell MALT lymphoma. Perifollicular distribution of centrocyte-like cells with a predominant monocytoid morphology.

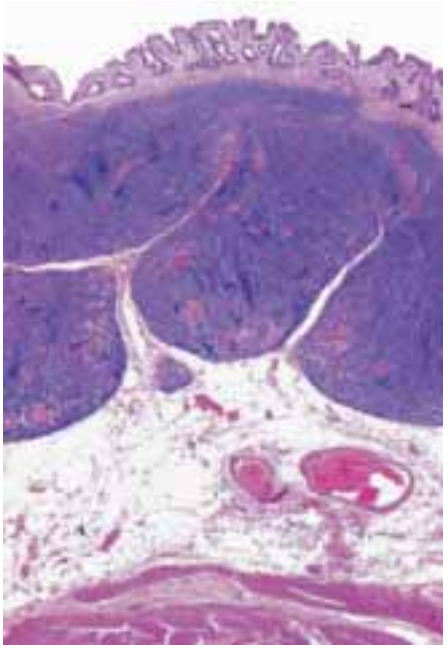

Fig. 3.40 Low-grade B-cell MALT lymphoma. Small lymphoid cells form a diffuse infiltrate extending into the submucosa.

cells, is due to a mechanism mediated via T-cells and that this help is contact dependant. Further studies have shown that the T-cells responsible for the proliferative drive are specifically those found within the tumour and their function cannot be replaced by T-cells derived from elsewhere (e.g. the spleen) in the same patient {769}.

Histopathology

The organisation of the lymphoma mimics that of normal MALT and the cellular morphology and immunophenotype is essentially that of the marginal zone B-cell. The neoplastic cells infiltrate between pre-existing lymphoid follicles, initially loca-lised outside the follicular mantle zone in a marginal zone pattern. As the lesion progresses, the neoplastic cells erode, colonize and eventually overrun the lymphoid follicles resulting in a vague nodularity to an otherwise diffuse lymphomatous infiltrate {800}. The morphology of the neoplastic cell can be variable even within a single case. Characteristically, the cell is of intermediate size with pale cytoplasm and an irregular nucleus. The resemblance of these cells to the centrocyte of the follicle centre has led to the term 'centrocyte-like (CCL)' cell being applied to the neoplastic component of MALT lymphomas. In some cases, the CCL cell may be more reminiscent of a mature small B lymphocyte while in other cases, the cell may have a monocytoid appearance with more abundant, pale cytoplasm and a well defined cell border. Plasma cell differentiation is typical and may be very prominent. Dutcher bodies may be identified. The CCL cells infiltrate and destroy adjacent gastric glands to form lymphoepithelial lesions. Lympho-epithelial lesions typical for MALT lymphoma are defined as infiltration of the glandular epithelium by clusters of neoplastic lymphoid cells with associated destruction of gland architecture and morphological changes within the epithelial cells, including increased eosinophilia.

Immunohistochemistry

The immunophenotype of the CCL cell is similar to that of the marginal zone B-cell. There is expression of pan-B-cell antigens such as CD20 and CD79a and the more mature B-cell markers CD21 and CD35. The cells do not express CD10. They are usually positive for bcl-2 protein and may express CD43 but do not express CD5 or CD23. They express surface and, to a lesser extent, cytoplasmic immunoglobulin (usually IgM or IgA, rarely IgG) and show light chain restriction. Immunostaining with anti-cytokeratin antibodies is useful in demonstrating lymphoepithelial lesions. Immunostaining with antibodies that highlight follicular dendritic cells (anti-CD21, anti-CD23 or anti-CD35) help to demonstrate underlying follicular dendritic cell networks in those cases in which the lymphoid follicles have been completely overrun by the lymphoma.

Differential diagnosis

The distinction between florid gastritis and low-grade MALT lymphoma may be difficult. In such cases it is essential to have sufficient biopsy material (up to eight biopsies from endoscopically suspicious areas) with good preservation of morphology and correct orientation of the biopsy specimen. For the distinction between reactive and neoplastic infiltrates, histological evaluation remains the gold standard, but accessory studies may be helpful. In both reactive and neoplastic cases, lymphoid follicles are present and these may be associated with active inflammation, crypt abscesses and reactive epithelial changes. In gastritis, the infiltrate surrounding the lymphoid follicles in the lamina propria is plasma cell predominant while in MALT lymphoma the infiltrate contains a dominant population of lymphocytes with CCL cell morphology, infiltrating through the lamina propria and around glands. Prominent lymphoepithelial lesions, Dutcher bodies and moderate cytological atypia are associated only with lymphoma. All of these features may not be present in biopsy material from a single case. In some cases it is justifiable to make the diagnosis of low-grade MALT lymphoma in the absence of one or more of these features if the overall histological appearances are those of lymphoma. Rare or questionable lymphoepithelial lesions, dense lymphoid infiltration, mild cytological atypia and muscularis mucosae invasion are features more often associated with, but not limited to, lymphoma {2212}.

In some cases it will not be possible to make a definite distinction between reactive infiltrates and lymphoma and in these cases a diagnosis of 'atypical lymphoid infiltrate of uncertain nature' is appropriate.

Effect of H. pylori eradication

The histological appearances of gastric biopsies from patients showing complete regression of lymphoma after *H. pylori*

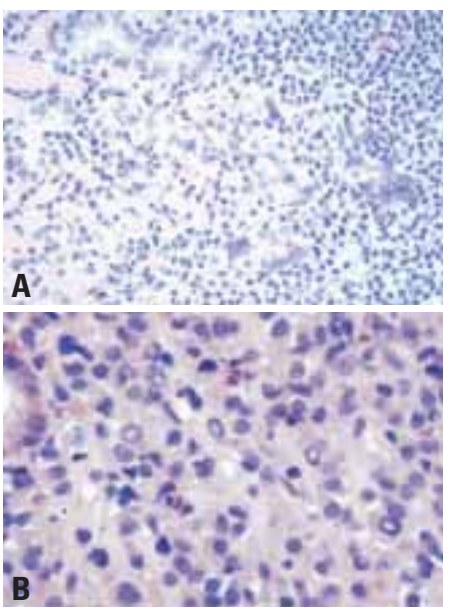

Fig. 3.41 Low-grade B-cell MALT lymphoma. The centrocyte-like cells show prominent plasma cell differentiation with **(A)** extracellular immunoglobulin deposition, and **(B)** prominent Dutcher bodies.

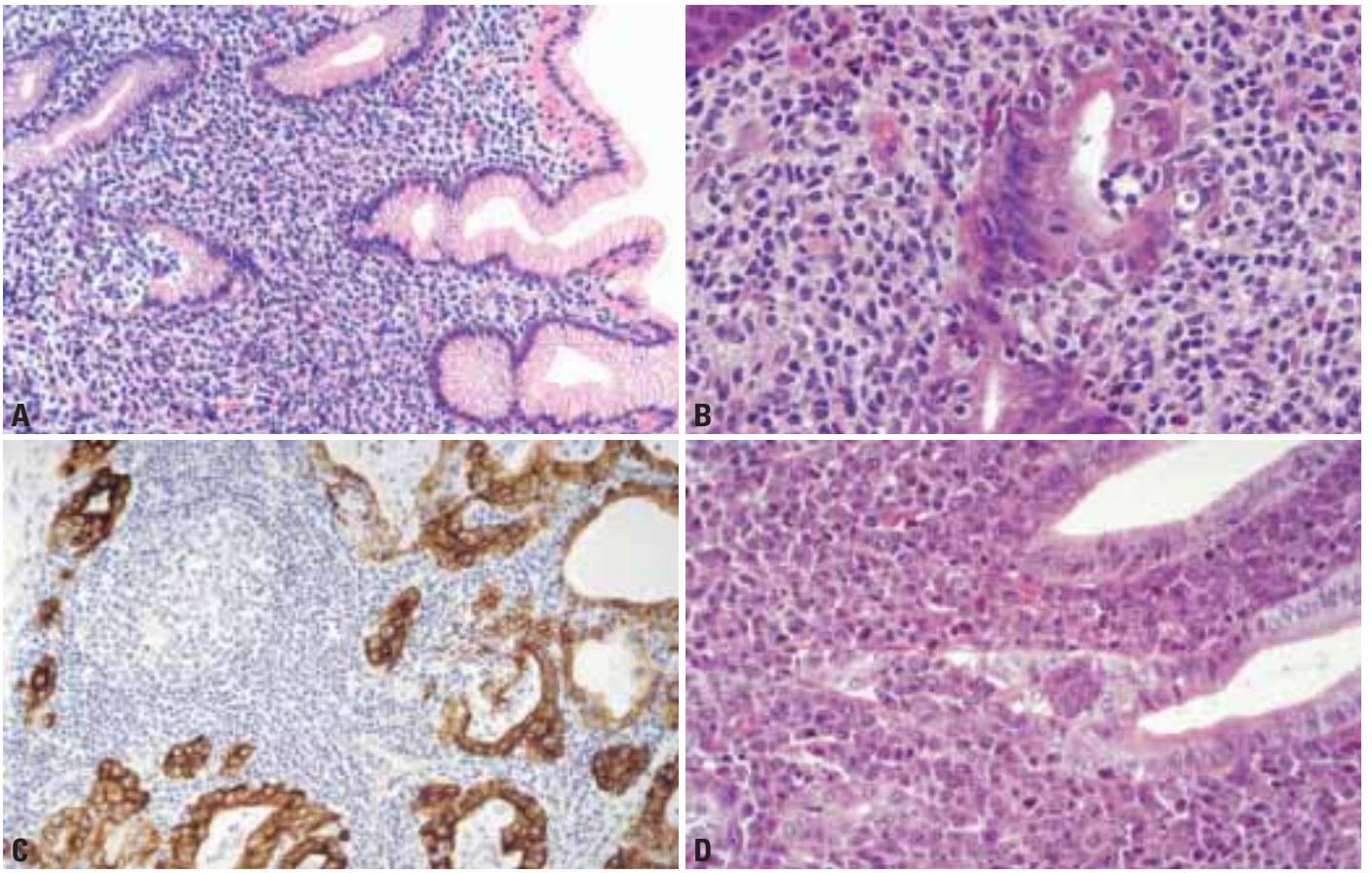

Fig. 3.42 A, B, C Low-grade B-cell MALT lymphoma. **A, B** Lymphoepithelial lesions. **C** Immunostaining for cytokeratin highlights lymphoepithelial lesions. **D** Diffuse large B-cell lymphoma; the neoplastic cells focally infiltrate glandular epithelium to form structures reminiscent of lymphoepithelial lesions.

eradication are characteristic. The lamina propria appears 'empty' with gland loss. Scattered lymphocytes and plasma cells are seen within the lamina propria and there are usually focal nodular collections of small lymphocytes. These collections frequently contain a mixture of B- and T-cells and may be based on follicular dendritic cell networks.

In most cases, the appearances are insufficient for a diagnosis of residual lymphoma. The significance of these lymphoid nodules remains uncertain. In cases showing partial regression or no change following *H. pylori* eradication, the lamina propria contains an infiltrate morphologically indistinguishable from that seen at diagnosis, but in these treated cases lymphoepithelial lesions may be very scanty or absent. In some cases of partial regression and in cases with relapsed low-grade MALT lymphoma following *H. pylori* eradication, the lymphoma may be largely confined to the submucosa with only minimal involvement of the mucosa.

PCR based diagnosis

The role of genetic analyses in the diagnosis and follow up of low-grade MALT lymphoma remains controversial. Up to 10% of well characterized cases of MALT lymphoma identified as clonal through demonstration of rearrangement of the immunoglobulin heavy chain gene by Southern blot fail to show a clonal pattern when examined for immunoglobulin heavy chain gene rearrangement by PCR using fresh frozen tissue {418}. This false negative rate increases if paraffin embedded material is studied {417}. Several studies have revealed by PCR the presence of clonal B-cell populations in biopsies from patients with uncomplicated chronic gastritis and no morphological evidence of lymphoma {1677, 225, 388}. In conjunction with histological assessment, PCR studies may be useful in monitoring regression of MALT lymphomas following conservative therapy {25}. However, PCR detected clonal B-cell populations may still be detected in cases showing complete histological regression. Some, but no all of these will eventually show molecular regression but there may be a prolonged time lag between histological and molecular regression {1677}. In the absence of histological evidence of residual lymphoma, the clinical significance of a persistent clonal population remains uncertain.

Progression to high-grade lymphoma

The emergence of clusters of large transformed 'blastic' B-cells reflects transformation to high-grade lymphoma {383}. Eventually, these areas become confluent to form sheets of cells indistinguishable from the cells of a diffuse large B-cell lymphoma. As long as a low-grade component remains, these tumours may be termed high-grade MALT lymphomas but during further progression, all traces of the pre-existing low-grade lymphoma are lost, making it impossible to distinguish the lesion from a diffuse large B-cell lymphoma of unspecified type. In cases with both low- and high-grade components, genetic studies have con-

firmed the transformation of low-grade to high-grade lymphoma in the majority of cases {1263} while in other cases both components appear clonally unrelated, suggesting the development of a second primary lymphoma {1184, 1491}.

Molecular genetics of MALT lymphomas

Early studies confirmed the presence of immunoglobulin gene rearrangement in each case {1803} and suggested that there was no involvement of the *bcl-1* or *bcl-2* oncogenes {2136}. The translocation t(11;18)(q21;q21) has been identified in a significant number of low-grade MALT lymphomas and may be the sole genetic alteration in these cases. However, this translocation appears to be less common in high-grade lesions {1435, 95}. Trisomy 3 has been detected in up to 60% of cases in some studies using both metaphase and interphase techniques {2134, 2137}, but this finding has not been confirmed by other studies {1434}. The translocation t(1;14) (p22; q32) has also been described in a small proportion of cases {2138} and this is associated with increased survival of tumour cells in unstimulated cell culture. Cloning of the breakpoint involved in this translocation has led to the discovery of a novel gene, *bcl-10,* on chromosome 1 that may be significant in determining the behaviour of MALT lymphomas {2116}.

Studies of the immunoglobulin gene of MALT lymphoma cells has shown the sequential accumulation of somatic mutations, consistent with an ongoing, antigen driven selection and proliferation {279, 434, 1546}. Study of the third complementary determining region of the immunoglobulin heavy chain gene shows a pattern of changes associated with the generation of antibody diversity and increased antigen binding affinity {131}.

Transformation of low-grade MALT lymphoma to a high-grade lesion has been associated with several genetic alterations. While the t(11;18) chromosomal translocation is not seen in high-grade MALT lymphoma and may be protective against transformation, alterations in the genes coding for p53, p16, c-myc and trisomy 12 have all been identified in high-grade lesions {1489, 1490, 1341, 270, 435, 1992}. Bcl-6 protein has also been described in high-grade lymphomas while being absent from low-grade lesions {1425}. Some studies have shown a high level of *bcl-6* gene hypermutations in diffuse large B-cell lymphomas independent of a rearrangement of the gene {1070}. Epstein-Barr virus is not associated with low-grade lymphomas and has only been seen in some high-grade lymphomas {1038, 1437}.

Mantle cell lymphoma

Mantle cell lymphoma of the stomach is typically a component of multiple lymphomatous polyposis of the gastrointestinal tract and infrequently encountered outside this clinical context {1380}. Morphologically and immunophenotypically, the lymphoma is indistinguishable from mantle cell lymphomas of lymph nodes, with a diffuse and monotonous infiltrate of cells with scanty cytoplasm and irregular nuclei that express B-cell markers together with CD5 and cyclinD1.

Other low-grade B-cell lymphomas

Although the lymphoid tissue in the stomach contains all the B-cell populations encountered in nodal lymphoid tissue, other low-grade B-cell lymphomas, such as follicle centre cell lymphomas, are very rare and usually indistinguishable from their nodal counterparts.

Diffuse large B-cell lymphoma

These lymphomas are morphologically indistinguishable from diffuse large B-cell lymphomas that arise within lymph nodes. There is complete destruction of the gastric glandular architecture by large cells with vesicular nuclei and prominent nucleoli. Variants of large B-cell lymphoma (e.g. plasmablastic lymphoma) may also be encountered {1541}.

Burkitt lymphoma

Although rare, classical Burkitt lymphomas may be encountered in the stomach {55}. The morphology is identical to that of Burkitt lymphoma encountered elsewhere, with diffuse sheets of medium sized cells with scanty cytoplasm and round/oval nuclei containing small nucleoli. Within the sheets there are numerous macrophages, giving a 'starry-sky' appearance. Mitoses are frequent and apoptotic debris abundant. The cells express CD10 in addition to pan-B-cell markers. Close to 100% of nuclei are immunoreactive for Ki-67.

T-cell lymphoma

Primary gastric T-cell lymphomas are rare. Most have been reported from areas of endemic HTLV-1 infection and probably represent gastric manifestations of adult T-cell leukemia/lymphoma (ATLL). In these regions, T-cell lymphoma may represent up to 7% of gastric lymphomas {1741}. Most of the remainder are similar to peripheral T-cell lymphomas encountered in lymph nodes but occasionally, gastric NK cell lymphomas are also seen {1741}. It has recently been demonstrated that some gastric T-cell lymphomas display features of intraepithelial T lymphocyte differentiation (e.g. expression of the human mucosal lymphocyte 1 antigen, CD103), similar to those seen in intestinal T-cell lymphomas {520}.

Hodgkin disease

Hodgkin disease may involve the gastrointestinal tract but this is usually secondary to nodal disease. Primary gastric Hodgkin disease is very rare {2210}.

Prognosis and predictive factors

Studies on the regression of low-grade MALT lymphoma through *H. pylori* eradication have shown remission in 67-84% of cases {1926, 1520, 2133}, but this applies only to low-grade lesions and is most effective for lesions showing superficial involvement of the gastric wall. Although remission following *H. pylori* eradication has occasionally been seen in advanced tumours, the highest success rate of 90-100% is seen in tumours confined to the mucosa and superficial submucosa. The time taken to achieve remission in these patients varies from 4-6 weeks to 18 months. The stability of these remissions remains to be determined; one study has reported a relapse in 10% of patients after a mean follow-up period of 24 months {1338} while others have found sustained remissions for up to six years {801}.

Surgical resection is associated with prolonged survival {552} in many cases. Involvement of the resection margins and advanced stage are poor prognostic features, but not with the addition of chemotherapy {1262}. Irrespective of treatment modality, the only significant independent prognostic variables are stage and tumour-grade {260, 1653, 1262, 320, 383}.

Mesenchymal tumours of the stomach

M. Miettinen
J.Y. Blay
L.H. Sobin

Definition

Most gastrointestinal mesenchymal neoplasms are gastrointestinal stromal tumours (GIST) or smooth muscle types. They are predominantly located in the stomach. The definitions of other mesenchymal lesions follow the WHO histological classification of soft tissue tumours {2086}.

Terminology

The designation GIST was originally introduced as a neutral term for tumours that were neither leiomyomas nor schwannomas. The term GIST is now used for a specific group of tumours comprising the majority of all gastrointestinal mesenchymal tumours. These tumours encompass most gastric and intestinal mesenchymal tumours earlier designated as leiomyoma, cellular leiomyoma, leiomyoblastoma and leiomyosarcoma {80, 76, 78, 79, 1227}. Currently, the terms leiomyoma and leiomyosarcoma are reserved for those tumours that show smooth muscle differentiation, histologically or by immunohistochemistry, e.g. with strong and diffuse actin and desmin positivity. Most tumours historically called leiomyosarcoma {31, 1559, 1750} are now classified as GISTs; hence the old literature on gastric (and intestinal) leiomyosarcomas largely reflects GISTs.

Epidemiology

GIST accounts for 2.2% of malignant gastric tumours in SEER data. There is no gender preference (M:F, 1.1:1), in contrast to carcinomas which have a M:F of 2:1 {1928}. Adults between the 6th and 8th decade are primarily affected. The ratio of the age-adjusted incidence rates for Blacks and Whites is greater for sarcomas (3 to 1) than for carcinomas (2 to 1). Black women are affected six times more frequently than white women (0.6 versus 0.1 per 100,000 per year, analogous to the ratio for uterine leiomyosarcomas) {1584}.

Localization

GISTs occur at every level of the tubular gastrointestinal tract and additionally may be primary in the omentum and mesentery. They are most common in the stomach (60-70%), followed by small intestine (20-30%), colorectum and oesophagus (together < 10%) {1227}.

Clinical features

GISTs present a spectrum from clinically benign, small to medium-sized tumours, to frank sarcomas. According to our estimate, approximately 30% of GISTs are clinically malignant, and a substantial number of patients with apparent radical surgery will relapse {1344, 462}. Typical of the malignant GISTs at all locations is intra-abdominal spread as multiple tumour nodules, and distant metastases most commonly to liver followed by lung and bone in decreasing frequency {478A, 1984, 1855}. Vague abdominal discomfort is the usual complaint in symptomatic tumours. Both benign and sarcomatous GISTs that project into the lumen may ulcerate and be a source of bleeding {80, 78, 79}.

Macroscopy

Small gastric GISTs appear as serosal, submucosal or intramural nodules that are usually incidental findings during abdominal surgery or endoscopy. Some tumours may ulcerate, especially the epithelioid stromal tumours. The larger tumours protrude intraluminally or to the serosal side, and may have a massive extragastric component that masks the gastric origin. Intraluminal tumours are often lined by intact mucosa, but ulceration occurs in 20-30% of cases. Infiltration by direct extension to the pancreas or liver occurs. On sectioning GISTs vary from slightly firm to soft, tan, often with foci of haemorrhage. Larger tumours may undergo massive haemorrhagic necrosis and cyst formation leaving only a narrow rim of peripheral viable tissue; malignant tumours may form complex cystic masses. Multinodular peritoneal seeding is typical of malignant GISTs.

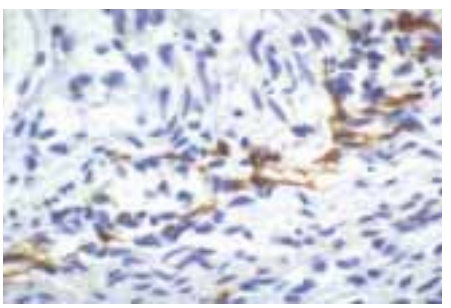

Fig. 3.43 Cajal cells immunoexpress KIT antigen (CD117) in fetal small intestine.

Histopathology

Typically GISTs are immunohistochemically positive for KIT tyrosine kinase receptor (stem cell factor receptor), which is perhaps their single best defining feature {920, 713, 1665, 1762}.

The c-kit positivity of GISTs parallels that seen in the interstitial cells of Cajal, the pacemaker cells regulating autonomic motor activity {1139, 1654}. Based on this, and on the expression of an embryonic form of smooth muscle myosin heavy chain in GISTs and Cajal cells {1648} the origin from Cajal cells has been proposed {920, 1762}. However, considering the origin of Cajal cells and smooth muscle from a common precursor cell {1035, 2186}, the hybrid Cajal cell and smooth muscle differentiation seen in many GISTs, and the occurrence of GISTs in the omentum and mesentery {1225}, their origin from such a precursor cell pool with differentiation towards a Cajal cell phenotype is more likely. Electron microscopic observations showing hybrid autonomic nerve and smooth muscle features in many GISTs are also consistent with origin from a multipotential precursor cell {474, 1227}.

Morphology. GISTs may resemble smooth muscle tumours histologically as well as grossly. The majority of gastric GISTs are spindle cell tumours that show a variety of histological patterns {1866}. Some, including many of the smaller ones, are collagen-rich and paucicellular. A perinuclear vacuolization pattern is common. Tumours with moderate cellularity and focal nuclear palisading can resemble nerve sheath tumours. Peri-

Fig. 3.44 Radiograph demonstrating mass defect in stomach due to a stromal tumour.

vascular hyalinization can accompany myxoid change. The epithelioid pattern occurs in approximately one-third of gastric GISTs and corresponds to tumours previously designated as leio-myoblastoma or epithelioid leiomyosarcoma. Some of the epithelioid tumours show mild pleomorphism. Marked pleomorphism is rare.

Immunohistochemistry. Most GISTs are positive for KIT (CD117), which may show membrane, diffuse cytoplasmic or a perinuclear accentuation pattern. Approximately 70-80% of GISTs are positive for CD34 (typically membrane pattern). 30-40% are focally or diffusely positive for α-smooth muscle actin, very few show reactivity for desmin (< 5%), and very few for S100-protein (< 5%, usually weak reactivity) {526, 1229, 1260, 1991, 1227, 1232}.

Assessment of malignancy and grading. Histological assessment of malignancy is essentially based on mitotic counts and size of the lesion. Tumours less than 5 cm are usually benign. Different limits have been applied for low-grade malignant tumours. This designation has been used for tumours showing mitotic counts greater than 5 per 50 HPF, or tumours showing as many as 5 mitoses per 10 HPF. Tumours over 5 cm, but with fewer than 5 mitoses per 50hpf, are often assigned to the category of 'uncertain malignant potential'. However, large tumours (especially over 10 cm) with no detected mitotic activity may develop late recurrences and even metastases. DNA-aneuploidy, high proliferative index (over > 10%) by proliferation markers (especially Ki67 analogs, such as MIB1) may reflect higher malignant potential {338, 362, 929, 525, 1048, 1632, 461, 462}.

Histological grading follows the systems commonly used for soft tissue sarcomas. Mitotic activity is the main criterion, namely those tumours with over 10 mitoses per 10 hpf are considered high-grade. Lower mitotic activity (over 1-5 mitoses/10 HPH) is considered low-grade.

Genetics

Both benign and malignant GISTs commonly show losses in chromosomes 14 and 22 in cytogenetic studies and by comparative genomic hybridization. Losses in 1p and chromosome 15 have been shown less frequently. Gains and high level amplifications occur in malignant GISTs in 3q, 8q, 5p and Xp {450, 451}.

A proportion of GISTs, more commonly the malignant examples, show mutations in the regulatory juxtamembrane domain (exon 11) of the *c-kit* gene. A family with germline KIT mutations and GISTs has also been described. These *c-kit* mutations have been shown to represent gain-of-function mutations leading to ligand-independent activation (autophos-

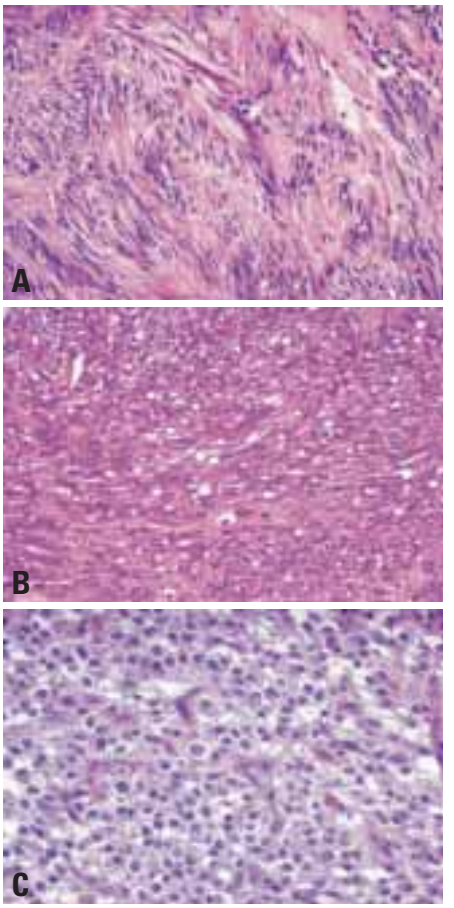

Fig. 3.46 Benign stromal tumours. **A** Vague palisading pattern reminiscent of a nerve sheath tumour. **B** Spindle cells with prominent cytoplasmic vacuolation. **C** An epithelioid pattern corresponding to the previous designation of leiomyoblastoma.

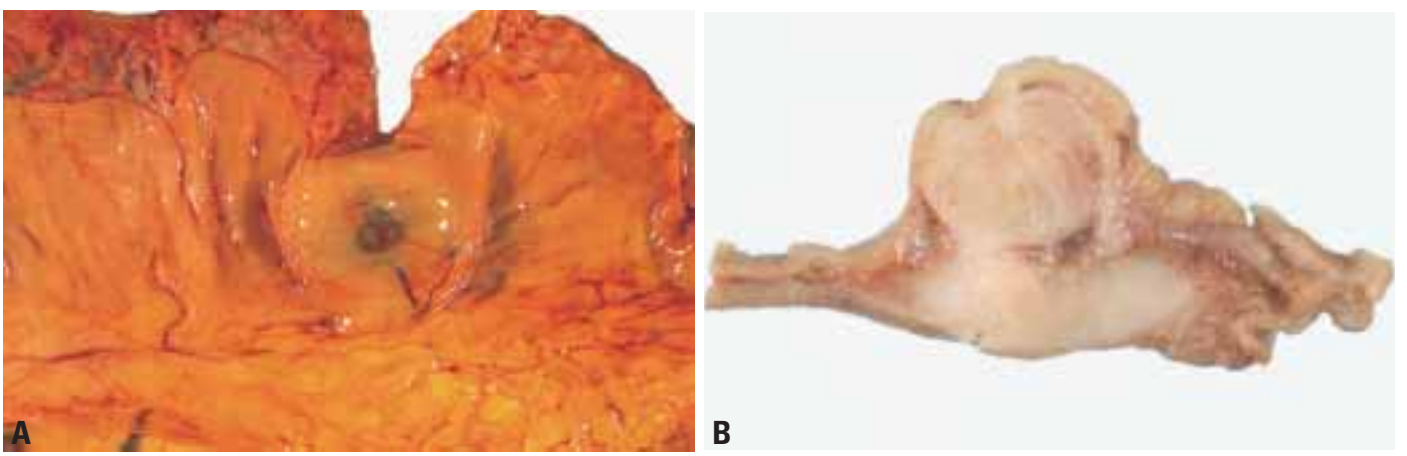

Fig. 3.45 Gastrointestinal stromal tumour. **A** Ulceration is present at the summit of the lesion. **B** Cut surface showing transmural extension.

Fig. 3.47 Examples of mutations of the exon 11 of the *c-kit* gene in gastrointestinal stromal tumours. **A** Nucleotide sequence of the *c-kit* gene. **B** Predicted amino acid sequences of the mutant KIT. The top line in each figure represents the germline I and the wild type KIT protein, respectively. Each line below them re-presents one case. The codons are indicated by numbers. The shaded areas correspond to deletions (black) or point mutations (gray). Courtesy of Dr. J. Lasota, Washington D.C.

phorylation) of the tyrosine kinase and further the phosphorylation cascade that leads into mitogenic activation {928, 713, 1310, 1356}. The most common mutations appear to be in-frame deletions of 3-21 base pairs, followed by point mutations and occasionally described insertions {475, 713, 1018, 1289}. Association of neurofibromatosis type I has been described in rare cases; these tumours represent phenotypical GISTs, but molecular genetic studies are not available {1681A}. The rare combination of pulmonary chondroma, gastric epithelioid GIST and paraganglioma in the Carney triad has probably a common yet unknown genetic link {246}.

Prognosis and predictive factors

The prognosis of GISTs is largely dependent on the mitotic rate, size, depth of invasion, and presence or absence of metastasis {462}. Although race and gender did not play a role in survival rates in the SEER data for gastric carcinomas, the 5-year survival rates for sarcomas varied considerably, e.g. 49% 5-year survival for males versus 74% for females; 37% for Blacks versus 66% for Whites {1928}.

Other mesenchymal tumours

Gastrointestinal autonomic nerve tumour (GANT)

Gastrointestinal autonomic nerve tumour (GANT), or the previous designation plexosarcoma, has been applied to mesenchymal tumours that have shown ultrastructural features of autonomic neurons:

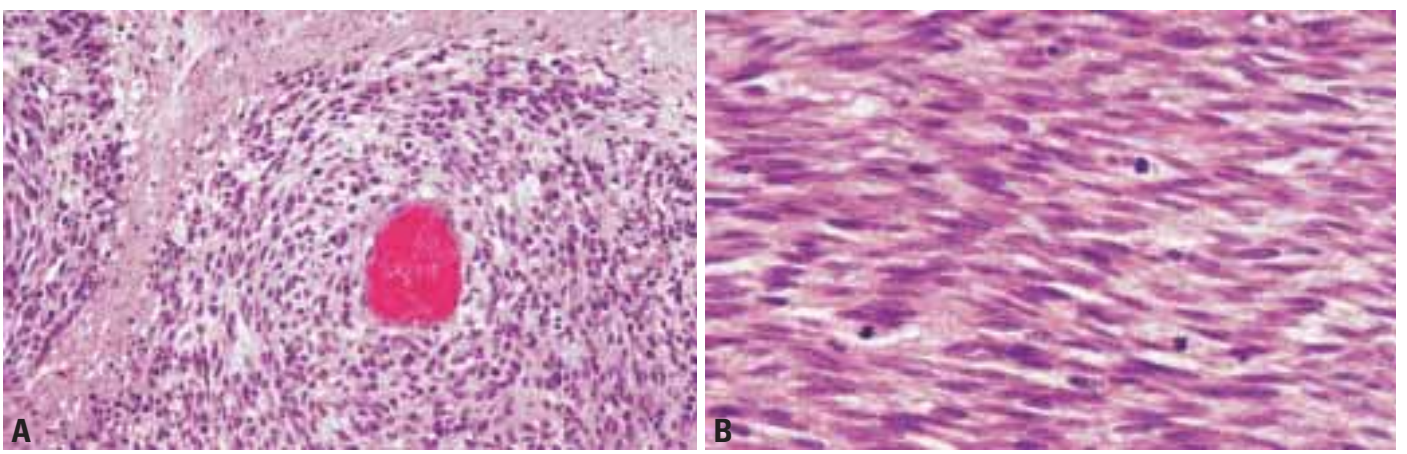

Fig. 3.48 Malignant gastrointestinal stromal tumours. **A** Tumour cells form perivascular collars surrounded by necrosis. **B** Numerous mitotic figures are present.

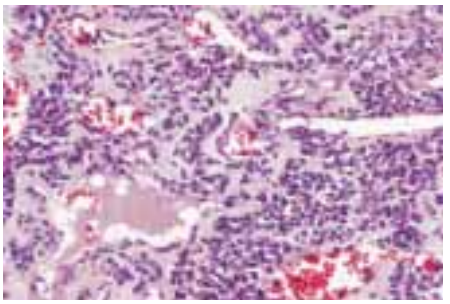

Fig. 3.49 Glomus tumour. Uniform tumour cells and dilated thin-walled blood vessels.

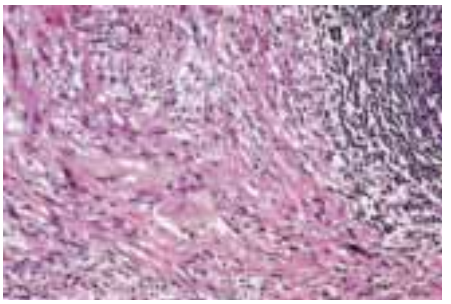

Fig. 3.50 Gastric schwannoma including part of the lymphoid cuff.

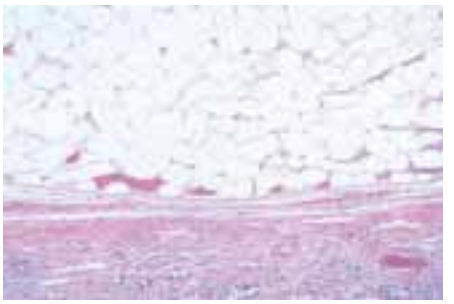

Fig. 3.51 Gastric lipoma.

cell processes with neurosecretory type dense core granules and arrays of microtubules {702, 701, 1023, 2038}. Histologically, such tumours have shown a variety of spindle cell and epithelioid patterns similar to those seen in GISTs; at least some of these tumours are positive for KIT. It therefore appears that GANT and GIST groups overlap, and may even merge. Because electron microscopy is currently applied less widely for tumour diagnosis than before, GAN-type differentiation in gastrointestinal tumours is probably underestimated. Correlative light microscopic, ultrastructural, immunohistochemical and molecular genetic studies are needed to resolve the question of the relationship of GANT and GIST.

Leiomyoma and leiomyosarcoma

Well-documented true gastric leiomyomas and leiomyosarcomas are so infrequent that there is no significant data on demographic, clinical or gross features. Leiomyomas are composed of bland spindle cells showing low or moderate cellularity and slight if any mitotic activity. There may be focal nuclear atypia. The cells have eosinophilic, fibrillary, often clumped cytoplasm. Leiomyosarcomas are tumours that show histologically and immunohistochemically evident smooth muscle differentiation. They usually present in older age and are typically of high-grade malignancy. As defined here, leiomyomas and leiomyosarcomas are typically globally positive for desmin and smooth muscle actin, and are negative for CD34 and CD117 (KIT). Tumours with mitotic counts exceeding 10 mitoses per 10 high power fields are classed as high-grade.

Glomus tumours

Lesions similar to glomus tumours of peripheral soft tissue occur predominantly in the gastric antrum as small intramural masses (1-4 cm in diameter, average 2 cm). They occur in older adults (mean 6th decade) with equal sex incidence {77}. One-third manifests as ulcer, one-third as bleeding, and one-third is asymptomatic. The lesions are often surrounded by hyperplastic smooth muscle and have sheets of rounded or epithelioid cells with sharp cell borders outlined by well-defined basement membranes demonstrable by PAS-stain or immunostaining for basement membrane proteins such as laminin and collagen type IV.
The tumour cells have small, uniform nuclei and mitotic activity is virtually absent. The tumour cells are positive for smooth muscle actin and negative for keratins. Multiple glomus tumours with apparent intravascular spread have been described {666}.

Schwannomas

These lesions are rare in the gastrointestinal tract, but the stomach is their most common site within the digestive system. They are not associated with neurofibromatosis types I or II and occur predominantly in older adults (average 58 years in the largest series). They grossly and clinically resemble GISTs. Schwannomas are usually covered by intact mucosa and principally involve the muscularis propria. The tumours vary from 0.5-7 cm (mean 3 cm) in diameter, and are spherical or ovoid, occasionally showing a plexiform multinodular pattern. Histologically, gastrointestinal schwannomas usually show a spindle cell pattern like cellular schwannoma with vague nuclear palisading. The tumours often have sprinkled lymphocytes and a nodular lymphoid cuff {366, 1666}. The distinction between schwannoma and GIST is important because the former is benign even when large and mitotically active. Schwannomas are positive for S100-protein and negative for desmin, actin and KIT.

Lipoma

Lipomas composed of mature adipose tissue may be observed in the stomach. They typically protrude into the lumen.

Granular cell tumour

Lesions similar to those in peripheral soft tissues are occasionally encountered in the stomach, where they principally occur as small submucous nodules and less commonly as intramural or subserous masses. These lesions occur predominantly in middle age, and show a strong predilection for Blacks. Associated gastric ulcer symptoms are common. See chapter on mesenchymal tumours of the oesophagus for pathological features {862}.

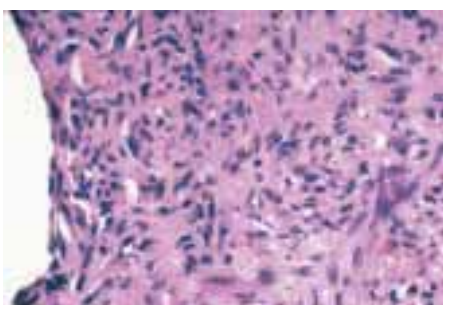

Fig. 3.52 Kaposi sarcoma of the stomach.

Kaposi sarcoma

Kaposi sarcoma may occur in the stomach as a mucosal lesion or, less commonly, as a mural mass, usually in HIV-positive patients.

Secondary tumours of the stomach

C. Niederau
L.H. Sobin

Definition

Tumours of the stomach that originate from an extra-gastric neoplasm or which are discontinuous with a primary tumour elsewhere in the stomach.

Incidence

Metastatic disease involving the stomach is unusual. An autopsy study from the USA found 17 metastases to the stomach in 1010 autopsies of cancer patients, giving a frequency of 1.7% {1220}. In a large series of autopsies from Malmö (Table 3.02), 92 gastric metastases were found in 7165 patients (1.28%) who had cancer at the time of death {130}.

Clinical features

Gastrointestinal symptoms may occur in up to 50% of patients with gastric metastases. Bleeding and abdominal pain are the most common clinical features, followed by vomiting and anorexia. Intestinal and gastric metastases were found after a median interval of 6 years (range, 0.12-12.5 years) following the diagnosis of primary breast cancer {1700}. Gastric metastasis from a breast cancer has occurred up to 30 years after diagnosis of the primary neoplasm {1148}. Occasionally, metastatic breast cancer in the stomach is detected before the primary tumour is diagnosed.

Imaging and endoscopy

An upper gastrointestinal endoscopy study identified 14 metastatic tumours in the upper gastrointestinal tract, 13 of which were in the stomach {873}. Many metastases are described as volcano-like ulcers {618; 1108}. On endoscopy, pigmentation may not be evident in some melanomas {1069}. In patients with metastatic lobular breast carcinoma the endoscopic appearance may be that of linitis plastica. In such cases, conventional biopsies may be too superficial to include diagnostic tissue in the submucosa. Endosonography may help direct attention to the deeper infiltrate {1097}. Gastric melanomas often appear as polypoid or target lesions on barium X-ray studies {1718} and, less commonly, as a submucosal mass {1148}.

Fig. 3.53 Multiple gastric metastases from rhabdomyosarcoma of the spermatic cord in a 15-year old boy.

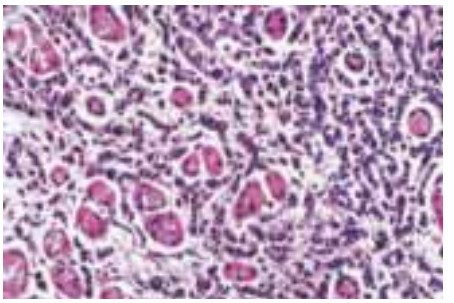

Fig. 3.54 Metastatic lobular carcinoma of the breast. Typical single file growth pattern.

Origin

In a large Swedish autopsy series {130} , most gastric metastases were from primary breast cancer, followed by melanoma and lung cancer (Table 3.02). There were gastric metastases in 25 of 695 (3.6%) patients with breast cancer, whereas gastric metastases were found in 10 of 747 (1.3%) of patients with lung cancer (see Table 4.01) {1220}. Several studies have shown lung, breast, other gastrointestinal carcinomas, and melanoma to be the most frequent primary lesions {1220, 158, 873, 618}. Less frequently, cancers of the ovary, testis, liver, colon, and parotid metastasize to the stomach {1220; 618; 1148; 1872}.

Of all the primary cancers that can lead to gastric metastasis, breast cancer does so most frequently. Some reports show that between 50% and 75% of patients with breast cancer develop gastric metastases {1148; 455}. However, in a Dutch study covering a 15-year-period, there were only 27 patients with gastric metastases from primary breast cancer {1872}.

There is no preferential localization of metastases to subsites in the stomach. Cancers at any site can produce gastric metastases through haematogeneous spread. Lesions of the pancreas, oeso-

Table 3.02
Metastases to the stomach, small intestine, colon and appendix. Data are from 16,294 autopsies {130}.

Site of metastasis	No. of cases with metastasis	% of all autopsies	Most frequent primary cancer	Next most frequent primary cancer
Stomach	92	0.58%	Breast (25 cases)	Melanoma (19)
Small intestine	125	0.78%	Lung (33 cases)	Melanoma (33)
Colon	62	0.39%	Lung (14 cases)	Breast (10)
Appendix	7	0.04%	Breast (2 cases)	Various

phagus and gallbladder can extend into the stomach by direct spread or, in some cases, by lymphatic spread. Ovarian adenocarcinoma usually spreads via the peritoneum and lymphatic channels; however, gastric metastases from ovarian cancer could also be of haematogenous origin [1148].

Macroscopy

Gastric metastases may appear as ulcers, as linitis plastica, or as polyps. The submucosal infiltration and extent of metastasis may be much more extensive than seen by endoscopy or radiography. Melanomas may or may not be pigmented.

Histopathology

The histopathology of gastric metastases is similar to that of the primary cancer and to other haematogenous metastases of that cancer. Immunohistochemical and molecular markers may help to differentiate a signet-ring cell carcinoma of the stomach from metastatic mammary disease [2174].Gastric metastasis from primary breast cancer is usually of lobular rather than ductal type [1872; 1097; 517].

Prognosis and predictive factors

Gastric metastases usually represent a late, disseminating stage of the disease in which other haematogenous metastases are also frequently found. The prognosis is therefore poor. In one series, the mean survival was 11 months, with a range of 3 months to 5 years [158] but the gastric metastases led to death in only 4 of 67 cases [618].

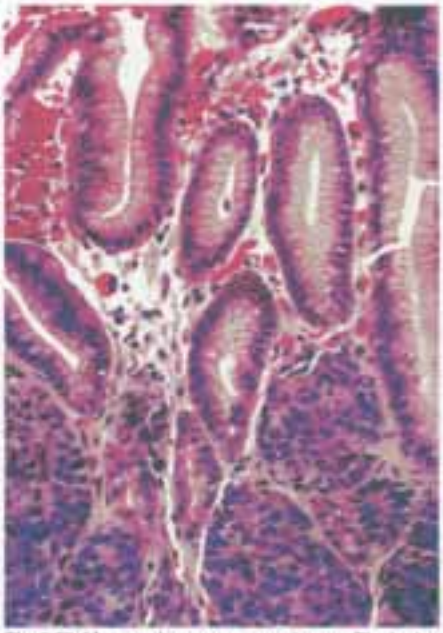

Fig. 3.55 Metastatic prostate carcinoma. The lesion resembles carcinoid. Tumour cells were positive for prostate specific antigen, negative for chromogranin.