Pathology of Gastric Cancer

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Abbreviations

GEJ	Gastroesophageal junction
EBV	Epstein–Barr Virus
FAP	Familial Adenomatous polyposis
HNPCC	Hereditary nonpolyposis colorectal cancer
MSI	Microsatellite instability
LGD	Low-grade dysplasia
HGD	High-grade dysplasia
WHO	World Health Association
EGC	Early Gastric Cancer

Introduction

Although the incidence of gastric cancer has steadily declined in past decades, gastric cancer remains the second leading cause of death from cancer worldwide. There is wide variation in the incidence of gastric carcinoma across different continents, with the highest rates in Asia, central Europe, and South America. In the USA, gastric cancer is the seventh most frequent cause of cancer-related death [1]. In the past several decades, changes in clinical practice have led to the diagnosis of a higher proportion of superficial and early-stage gastric cancers, which now represents almost 20 % of all newly diagnosed cancers in the USA and 50 % in Japan [2–5]. The anatomic distribution of gastric cancer is also changing, with the incidence of proximal gastric tumors rising and currently representing approximately 30 % of all gastric cancers [6, 7].

Epidemiologic, anatomic location, pathogenic factors, as well as molecular and genetic factors, and patterns of clinical practice all contribute to these demographic differences. This chapter intends to focus on the pathologic aspect of the disease and its implications in diagnosis and management of gastric carcinoma.

Pathogenesis of Gastric Carcinoma

Reflux

It has been well established that gastroesophageal junctional (GEJ) mucosa is frequently associated with acid reflux from the stomach. Patients with cardia cancer share similar characteristic risk factors with those for GEJ adenocarcinoma, such as age of onset and age distribution, a higher male-to-female ratio, morphologic phenotypes, and ethnic differences in disease distribution [8–12]. The association of cardia cancer with Barrett's esophagus and gastroesophageal reflux disease is a subject of debate, since the definition of true cardia carcinoma can be challenging

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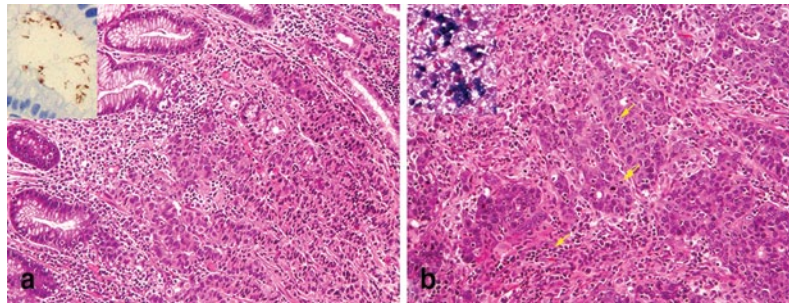

Fig. 4.1 *H. pylori* and Epstein–Barr virus infection associated gastric adenocarcinoma. **a** An adenocarcinoma arises in association with active chronic gastritis with *H. pylori* organisms identified on immunohistochemical stain (*insert*). **b** A poorly differentiated carcinoma with intense intraepithelial and stromal lymphocytic infiltration (*arrow*) and EBV genome is identified by in situ hybridization (*insert*)

when the tumor is large and involves the gastroesophageal junction [12]. As many as 70% of the cardia carcinomas have a component of intestinal metaplasia, an early pathologic process similar to that observed in Barrett's esophagus associated adenocarcinoma at the GEJ.

Interestingly, prior gastric surgery in male patients, particularly subtotal gastrectomy with Billroth II reconstruction is associated with an increased risk for the subsequent development of remnant gastric cancer, probably due to enterogastric reflux of bile and pancreatic secretions [13–16].

Infection

Helicobacter pylori infection is a major environmental cause of gastric cancer. Long-standing *H. pylori* infection induces chronic gastritis, which results in mucosal atrophy and intestinal metaplasia [17, 18] (Fig. 4.1a). There is a 4–9 fold increased risk of gastric neoplastic lesions among patients with *H. pylori* infection, particularly if infection began in early childhood [19–21]. Certain aspects of *H. pylori* virulence have been associated with risk of gastric cancer. In particular, the strains which are positive for cytotoxin-associated gene A (CagA) produce higher levels of interleukin 8 which elicit more intense inflammation. These strains are associated with an increased risk of gastric carcinoma [22]. However, gastric cancer does not develop in most individuals who have *H. pylori* infection, and other environmental and host factors are presumed to be important in the pathogenesis of this disease [23, 24].

Epstein–Barr virus (EBV) has long been recognized as a distinct pathogenic cause of gastric carcinoma [25, 26]. EBV is detected in about 10% of the gastric carcinoma cases (Fig. 4.1b). All tumor cells in EBV-associated gastric carcinoma harbor the clonal EBV genome. Gastric carcinoma associated with EBV occurs predominately in men and in younger-aged individuals. These carcinomas exhibit a unique histologic phenotype, genetic/epigenetic genotype, and distinct clinicopathological features [25, 27–29].

Autoimmune Gastritis

Autoimmune gastritis arises secondary to an immune-mediated destruction of parietal cells (pernicious anemia), is confined to the body and fundus of the stomach, and is characteristically associated with neuroendocrine cell (enterochromaffin-like cell) hyperplasia and neoplasia (Fig. 4.2). In patients with autoimmune associated atrophic gastritis, most adenocarcinomas are of the intestinal type and the risk of gastric cancer increases at least three fold [30]. In contrast, gastric type-1 neuroendocrine (carcinoid) tumors arising in autoimmune atrophic gastritis are relatively indolent in their behavior [31].

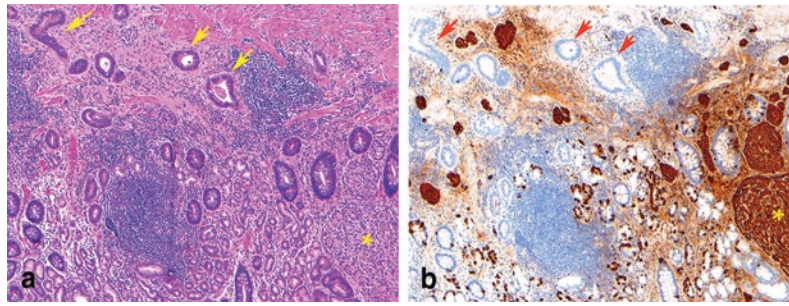

Fig. 4.2 Type-I gastric neuroendocrine tumor and the coexisting adenocarcinoma. Histopathology of a neuroendocrine tumor (*star*) exhibits a nested pattern (**a**) and the immunoreactivity for chromogranin (**b**) is present in the background of hyperplastic neuroendocrine cells and neuroendocrine tumor. A well differentiated and gland-forming adenocarcinoma (*arrow*) invades the muscularis mucosa and infiltrates the submucosa

Gene-Dietary Interaction

Environmental factors in addition to *H*. pylori infection, including cigarette smoking and diet, play an important role in gastric carcinogenesis [32]. Foods that are salted, smoked, pickled, and preserved foods rich in salt, nitrites, or preformed N-nitroso compounds are associated with an increased risk of gastric cancer [33].

Genetic polymorphisms may also contribute to the etiology of gastric cancer by altering the activity of enzymes that are involved in multiple molecular processes, such as DNA synthesis and repair, carcinogen metabolism, the inflammatory response, and tumor suppression [34]. Individuals who carry high-risk genetic variants and high-risk diets have an increased risk of gastric cancer compared with those who do not carry high-risk genetic variants or those with high-risk genetic variants but low-risk diets. Distinctive dietary patterns and regional variations in genetic polymorphisms may explain regional variations in gastric cancer incidence [35–37].

Hereditary

Approximately 10% of all gastric cancers are familial. Germline mutations in the E-cadherin CDH1 gene account for 30–40% of the rare syndrome known as hereditary diffuse gastric cancer, and gastric cancers also occur less frequently as a component of other hereditary cancer syndromes [38].

Familial Diffuse Gastric Carcinoma

Germline mutations in CDH1 are the molecular basis for familial gastric cancer syndrome [39–42] (Fig. 4.3a). Initially identified in three Maori families in New Zealand, at least 100 families have been reported to carry the CDH1 germline mutation [43]. Given the relatively high penetrance disease (70–80%) [44], a lifetime risk of developing gastric cancer of approximately 67% in men and 83% in women [45], prophylactic total gastrectomy is often considered after a familial diagnosis of a CDH1 mutation [46]

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome

After endometrial carcinoma, gastric carcinoma is the second most common extra-colonic cancer in patients with hereditary nonpolyposis colorectal cancer (HNPCC) (Fig. 4.3b). There is a four-fold relative risk of developing gastric cancer in HNPCC patients, with the risk predominantly in younger patients (11.3-fold in the 30s and 5.5-fold in the 40s). Additionally, the relative risk is greater in mutation carrier families than noncarrier families (3.2-fold versus 1.6-fold). The overall lifetime risk of developing gastric cancer is 10% for patients of Western ancestry and 30% for patients of Asian ancestry [54–57], and microsatellite instability (MSI) phenotype is noted in 65% of these cases.

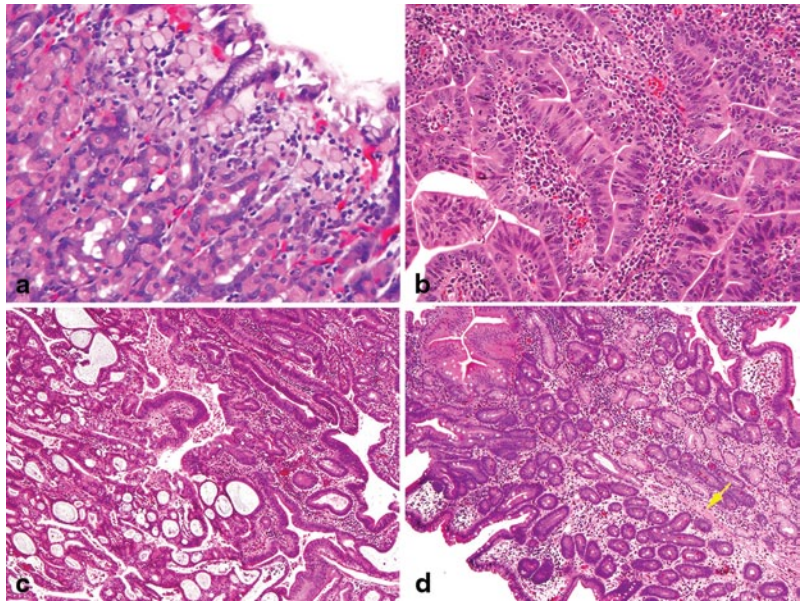

Fig. 4.3 Hereditary condition associated gastric neoplasms. **a** Early hereditary diffuse gastric carcinoma with signet ring cell morphology is present in the superficial lamina propria. **b** HNPCC (Lynch syndrome) associated intestinal type gastric adenocarcinoma exhibits increased intraepithelial and stromal lymphocytes. **c** An FAP associated adenocarcinoma (*left*) arises in a fundic gland polyp with dysplasia (*upper right*). **d** Gastric Peutz–Jeghers polyp is composed of irregular and architecturally distorted proliferation of foveolar glands with increased inflammation in the lamina propria and smooth muscle proliferation (*arrow*)

Familial Adenomatous Polyposis Coli (FAP)

Patients with familial adenomatous polyposis coli (FAP) also develop multiple gastric fundic gland polyps, which can undergo neoplastic transformation as a result of somatic mutations of the adenomatous polyposis coli (APC) gene [47] (Fig. 4.3c). However, in contrast to the development colon adenocarcinoma from adenomatous polyps in FAP patients, the development of gastric carcinoma in fundic gland polyps is rare [48–51]. Interestingly, there is a higher risk of neoplastic transformation in the stomach of Asian FAP patients as compared to Western FAP patients [52, 53].

Li–Fraumeni Syndrome

Germline mutations of the TP53 gene are present in 50–70% of the patients with Li–Fraumeni syndrome.The most common neoplasms in patients with Li–Fraumeni syndrome are soft tissue sarcoma, breast cancer, and brain tumors. While gastrointestinal tract tumors account for less than 10% of all Li–Fraumeni syndrome associated neoplasms, gastric carcinomas (which may be multiple) represent more than 50% of the gastrointestinal tumors in patients with Li–Fraumeni [58, 59].

Peutz–Jeghers Syndrome

Mutation of the serine/threonine–protein kinase 11 (STK11) gene, located on chromosome 19p13.3, is responsible for Peutz–Jeghers syndrome [60]. Characteristic gastrointestinal hamartomatous polyps develop (Fig. 4.3d), and these patients have an increased risk of gastric cancer, although the exact degree of risk is a subject of debate [61, 62].

Gastric Hyperplastic Polyposis

Gastric hyperplastic polyposis is an inherited autosomal dominant syndrome characterized by the presence of hyperplastic gastric polyposis, severe psoriasis, and an increased incidence of gastric cancer of the diffuse type [63, 64].

Precursors of Gastric Carcinoma

The well-defined chronic inflammation-intestinal metaplasia-glandular dysplasia—cancer sequence typically precedes the development of most intestinal type gastric adenocarcinomas [65]. While intestinal metaplasia proceeded by epithelial dysplasia (type I) may be present as a polypoid lesion and resemble a colonic adenoma, it is genetically distinct from the typical tubular adenoma in the colon. In contrast to adenoma-carcinoma sequence in colonic adenocarcinoma (which is usually associated with an intrinsic genetic abnormality in the APC molecular pathway) the progression of intestinal dysplasia to gastric adenocarcinoma occurs with a stepwise accumulation of multiple genetic abnormalities. True *de novo* gastric adenomas are rare outside the setting of FAP, in which gastric fundic gland polyps progress to epithelial dysplasia secondary to inherent APC gene abnormality. A less common histologic variant of dysplasia is gastric foveolar (type II) dysplasia with a gastric mucin phenotype [66]. The significance of these subtypes remains controversial and phenotyping of gastric dysplasia is not recommended at this time.

The natural history of gastric dysplasia depends on its grade, extent of dysplasia, and surface appearance (polypoid versus flat or depressed). Dysplasia is graded based on cytologic and ar-

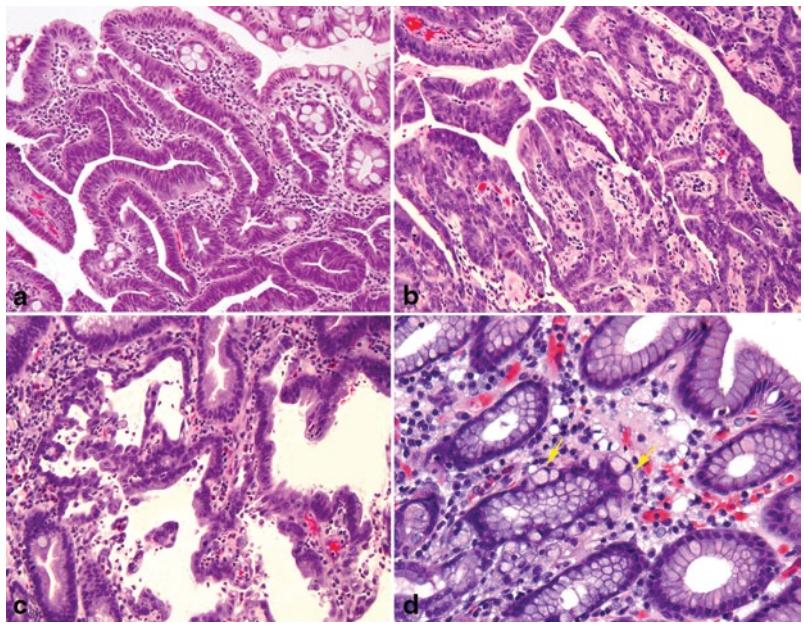

Fig. 4.4 Precursors of gastric adenocarcinoma. **a** Long standing chronic gastritis is followed by intestinal metaplasia (*upper right*) and low-grade glandular dysplasia which is demonstrated by nuclear elongation and pseudostratification. **b** High-grade dysplasia exhibits loss of cellular polarity of the epithelium with glandular crowding and architectural alteration which approaches the criteria of early carcinoma. **c** Even in the absence of invasion into the stroma, early adenocarcinoma proceeded from high-grade dysplasia is demonstrated by expansile crypt growth with cribriform complexity. **d** In situ signet ring cell carcinoma is present within the basal membrane with hyperchromatic and depolarized nuclei and pagetoid spread of signet ring cells (*arrow*)

chitectural features as either low grade (LGD) or high grade (HGD) (Fig. 4.4a, b). Low-grade dysplasia diagnosed on endoscopic biopsies has been shown to regress in 38–75% of the cases, to persist in 19–50%, and to progress to HGD in 0–9% of the cases [67]. The best independent predictors of progression to adenocarcinoma are lesions greater than 2 cm and a depressed configuration on endoscopic examination [68].

High-grade dysplasia regresses in only 0–16% of the cases, persists in 14–58%, and progresses in 10–100% to adenocarcinoma (Fig. 4.4c) [67]. Given the high probability of progression to adenocarcinoma, a lesion diagnosed as HGD on endoscopic biopsy should be considered for endoscopic mucosal resection if feasible or surgical resection if HGD is present as multifocal lesions or if endoscopic mucosal resection is not technically feasible.

The precursor of diffuse gastric carcinoma is thought to originate from oxyntic gland tubule neck (or globoid) dysplasia [69] in situ signet ring cell carcinoma. This corresponds to the presence of signet ring cells within the basal membrane, generally with hyperchromatic and depolarized nuclei and pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae (Fig. 4.4d) [70].

Pathologic Classification

Tumor Location

The location of gastric adenocarcinoma may, to some extent, reflect the pathogenesis of the disease. For example, intestinal type adenocarcinoma in the proximal stomach may be associated with a reflux etiology (Fig. 4.5a), while intestinal type adenocarcinoma in the distal stomach is more likely related with *H. Pylori* infection associated pathogenesis (Fig. 4.5b). Diffuse type gastric cancer is more commonly located in the middle third and body of the stomach (Fig. 4.5c), while remnant cancer is invariably located in the gastric mucosa at duodenogastric anastomosis (Fig. 4.5d). Determination of a precise tumor location can be challenging and even subjective, especially when the lesion is large and straddles multiple anatomical sites within the stomach. Nevertheless, documentation of the relative location of the tumor is important for the elucidation of potential pathogenesis and classification of the disease, as well as for the evaluation of the extent of the disease and the resection margin status.

Gross Pattern

The gross configuration of advanced gastric cancer can be classified using Borrmann classification, which designates gastric carcinomas into four distinct types[71]: polypoid (type I), fungating (type II), ulcerating (type III), and diffusely infiltrating (type IV). Diffusely infiltrating is also referred to as linitis plastica when it involves nearly the entire stomach and it is consistently associated with the diffuse histologic subtype. In contrast, types I, II, and III are associated with other histologic subtypes. Type II, the most common subtype, represents 36% of all gastric carcinomas and is frequently detected on the lesser curvature of the antrum. Types I and III each represent 25% of all advanced gastric carcinomas, and they are more common in the corpus, usually on the greater curvature.

Histologic Classification

Gastric cancer represents a heterogeneous group of tumors with diverse pathogenesis, morphologic features, and molecular backgrounds. While recent genomic analysis has identified several subtypes of gastric adenocarcinoma by their generic signatures [29], histopathologic classification remains critical for a number of clinical assessments of the disease and serves as the basis for the molecular classification of the disease [72, 73]. Several systems have been proposed to aid in the classification of gastric adenocarcinoma based on the microscopic futures of the tumor [74–76]. The two most commonly used histologic classifications are the Laurén classification and the World Health Organization (WHO) systems [77, 78]; significant correlation is seen between these two schemes [79].

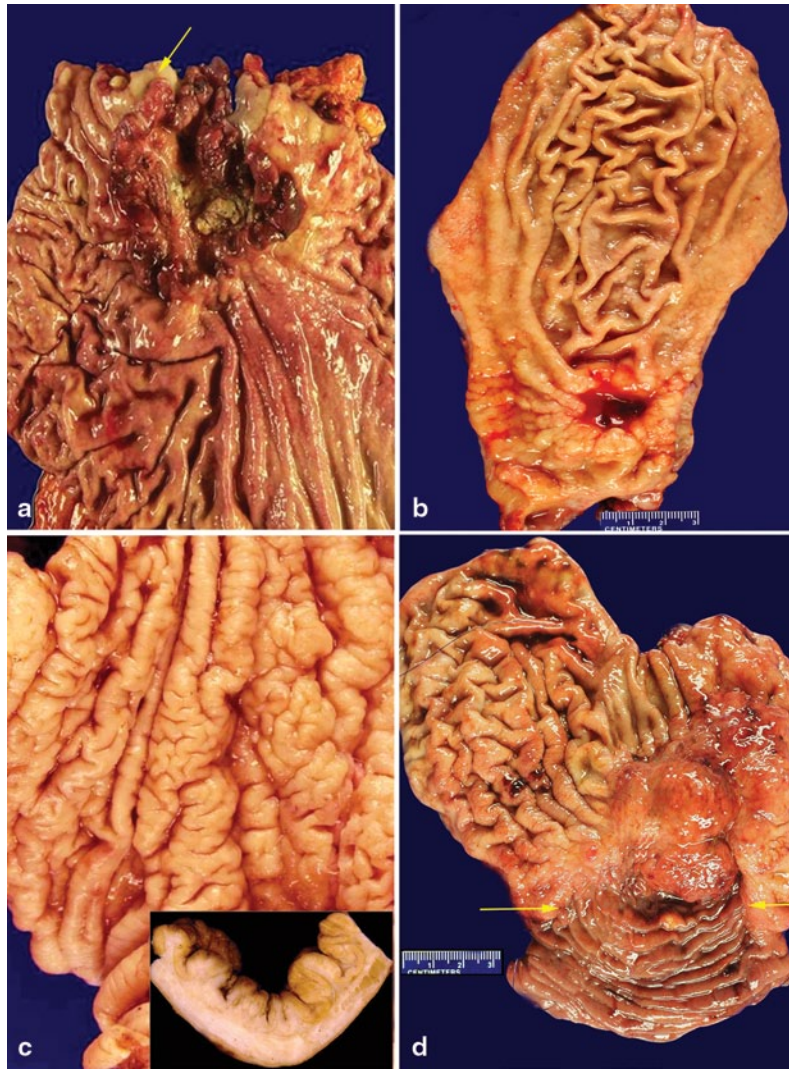

Fig. 4.5 Gross pathology of gastric adenocarcinoma. **a** A proximally located gastric adenocarcinoma with minimal extension into the squamous mucosa (*arrows*) of the esophagus. **b** An ulcerated intestinal carcinoma is located in the distal stomach. **c** A diffuse type adenocarcinoma is located in the body of the stomach with intact mucosa but rigid mucosal fold. A cross section of the mucosa reveals thickened gastric wall secondary to diffuse infiltration by tumor cells. **d** A remnant gastric cacumina is located in the gastric mucosa near the anastomotic line (*arrows*)

The Laurén classification separates gastric adenocarcinomas into two primary subtypes: intestinal and diffuse, and tumors exhibiting features of both the intestinal and diffuse types are designated as mixed-type adenocarcinoma (Fig. 4.6a, b, c, d). The intestinal type is characterized by the formation of glands exhibiting various degrees of differentiation either with or without extracellular mucin production (Fig. 4.6a). The diffuse type of gastric adenocarcinoma is composed of poorly cohesive cells without gland formation (Fig. 4.6b, c). This type of tumor often contains cells with intracytoplasmic mucin, known as "signet ring cells" (Fig. 4.6c), although this term has been synonymously used for diffuse cancer even in the absence of intracytoplasmic mucin (Fig. 4.6c). In addition to their distinct morphologic characteristic, the intestinal and the diffuse

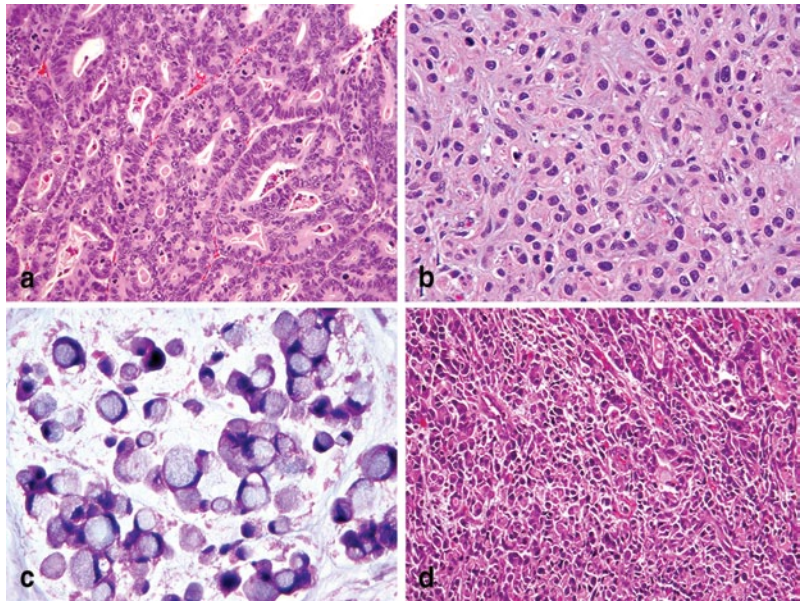

Fig. 4.6 Lauren's histopathology classification of Gastric Carcinoma. **a** Intestinal type adenocarcinoma with well-formed glandular and tubular architecture. **b** Poorly differentiated diffuse type adenocarcinoma. **c** Diffuse type adenocarcinoma with intracellular mucin and signet ring cell features. **d** Lauren's mixed type adenocarcinoma with a small component of poorly differentiated intestinal phenotype (*upper right*) and a poorly differentiated diffuse/poorly cohesive carcinoma with focal signet ring cell features (*left*)

subtypes of gastric adenocarcinoma also have different clinicopathologic features (Table 4.1).

While the basis for the initial Laurén classification was exclusively morphologic characteristics, accumulative knowledge in the epidemiology and pathogenesis of gastric carcinoma has indicated that this classification system is also valuable in defining molecular subtypes of gastric cancer [72, 73]. In the absence of significant chronic gastritis, intestinal metaplasia, or dysplasia, pure diffuse type of gastric cancer probably represents either a hereditary or sporadic ideology. However, significant components of diffuse or poorly cohesive carcinoma can be seen in mixed adenocarcinoma with inflammation-metaplasia-dysplasia-carcinoma precursors, often complicating molecular analysis of the tumor.

In 2010 the WHO revised its morphologic classification to reflect the patterns exhibited throughout the gastrointestinal (GI) tract [78]. This classification recognizes five major types of gastric adenocarcinoma based on the predominant histologic growth pattern: (1) papillary, (2) tubular, (3) mucinous (tumors with

Table 4.1 Clinical and pathologic features of Laurén subtype gastric adenocarcinoma

	Intestinal type	Diffuse type
Onset age	Older than 50 year	Younger than 50 years
Gender	Male > Female	Male = Female
Geographic distribution	Asia (China Japan, Korea)	Anywhere
Precursor lesion	Intestinal metaplasia/dysplasia	Signet ring cell carcinoma in situ
Common location	Antrum or cardia	Body
Borrmann classification	Type I, II, III	Type IV
Genetic association	HNPCC, AFP	Hereditary diffuse gastric cancer, hyperplastic polyposis

Table 4.2 WHO classification of carcinoma of the stomach [99]

Tumor type	Histologic features
Adenocarcinoma	
Papillary adenocarcinoma	Exophytic with elongated frond-like tumor extensions with fibrovascular cores; usually better differentiated and low grade
Tubular adenocarcinoma	Dilated or slit-like branching tubules; usually low, although poorly differentiated variants are not uncommon
Mucinous adenocarcinoma	Contains more than 50% extracellular mucin pools. May contain scattered signet-ring cells more commonly seen in proximal/cardia location
Poorly cohesive carcinomas, including diffuse and signet-ring cell carcinoma and other variants	Tumor cells infiltrate as isolated single cells or small aggregates. The carcinoma is predominantly composed of signet-ring cells containing a clear droplet of cytoplasmic mucin displacing the nucleus. Other variants of poorly cohesive carcinoma may resemble mononuclear inflammatory cells
Mixed carcinoma	Mixture of morphologically identifiable components such as tubular, papillary, and poorly cohesive patterns
Adenosquamous carcinoma	Mixture of glandular and squamous neoplastic components; the squamous component should comprise at least 25% of the tumor volume
Carcinoma with lymphoid stroma (medullary carcinoma)	Poorly developed glandular structures associated with a prominent lymphoid infiltrate in the stroma. Associated with EBV infection or HNPCC-associated carcinoma and may have a favorable prognosis
Hepatoid adenocarcinoma	Large polygonal eosinophilic tumor cells resembling hepatocytes; may express alpha-fetoprotein
Squamous cell carcinoma	Both Keratinizing and nonkeratinizing forms are encountered
Undifferentiated carcinoma	High-grade carcinoma that cannot be further classified as adenocarcinoma, squamous cell carcinoma, or other recognized variants
Neuroendocrine carcinoma	Poorly differentiated high-grade carcinoma with diffuse or focal synaptophysin chromogranin-A expression. These tumors exhibit a high mitotic rate (>20 per 10 high power field, and Ki67 is usually >50%) marked nuclear atypia, and may have focal necrosis
Large cell neuroendocrine carcinoma	Tumor cells are large, with moderate amount of cytoplasm, and may contain prominent nucleoli
Small cell neuroendocrine carcinoma	Tumor cells are small, with finely granular chromatin and indistinct nucleoli
Mixed adenoneuroendocrine carcinoma	Composed of both gland-forming and neuroendocrine malignant elements, with at least 30% of each component. Identification of scattered neuroendocrine cells in adenocarcinomas by immunohistochemistry does not qualify as mixed carcinoma

mucinous pools exceeding 50% of the tumor), (4) poorly cohesive (including signet ring cell carcinoma and other variants), and (5) mixed adenocarcinomas (Table 4.2). Uncommon variants of gastric carcinomas include the squamous cell, adenosquamous, hepatoid (Fig. 4.7a), micropapillary, carcinoma with lymphoid stroma (medullary carcinoma) (Fig. 4.7b), carcinoma with pancreatic acinar differentiation (Fig. 4.7c), choriocarcinoma [80, 81], undifferentiated subtypes (Fig. 4.7d), carcinoma with sarcomatous differentiation (Fig. 4.7e), high grade neuroendocrine carcinoma of small cell or large cell subtype (Fig. 4.7f), and carcinoma arising in gastric heterotopia in the esophagus (gastric inlet) or pancreatic heterotopia. The so called medullary carcinoma usually has an expansile growth pattern with intratumoral and peritumoral lymphocytic infiltration; this tumor phenotype is commonly associated with either EBV or microsatellite instability associated gastric carcinoma. The relevant clinical implication when encountering these rare subtypes of gastric carcinoma is that a metastasis should be excluded before entertaining a diagnosis of primary gastric carcinoma. In addition, any histologic subtype of gastric carcinoma, when poorly differentiated, can present with either partial or entirely sarcomatous features (sarcomatoid carcinoma) (Fig. 4.7e), which

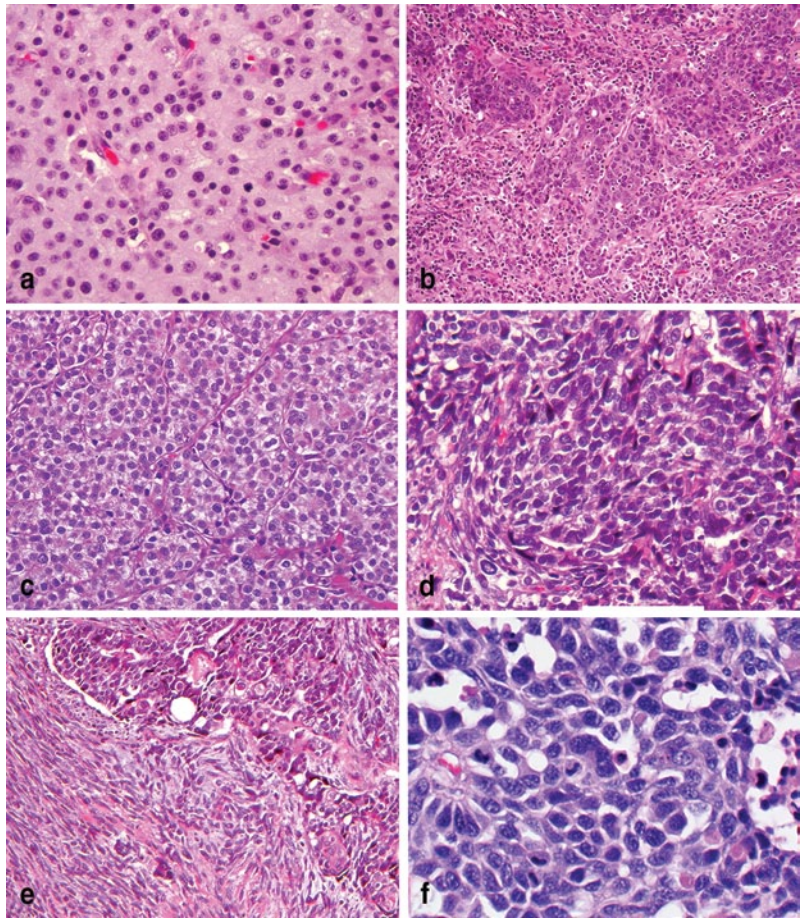

Fig. 4.7 Uncommon histopathologic variants of gastric adenocarcinoma. **a** Adenocarcinoma with hepatoid features. **b** Medullary adenocarcinoma with markedly increased intraepithelial and stroma lymphocytes (*small blue cells*). **c** Adenocarcinoma with prominent pancreatic acinar differentiation. **d** Undifferentiated carcinoma. **e** Undifferentiated carcinoma (*upper right*) with sarcomatous differentiated (*low left*). **f** High grade neuroendocrine carcinoma, small cell type

is not uncommon in the upper gastrointestinal tract or the pancreaticobiliary carcinoma.

Diagnostic Issues

Primary Versus Metastasis

The pathologic diagnosis of gastric adenocarcinoma, particularly a poorly differentiated and nonintestinal subtype, can be challenging with a biopsy specimen. While stomach is not a common site for metastasis, a number of epithelioid neoplasms can metastasize to the gastric mucosa and the differential diagnosis between a primary gastric carcinoma and a metastasis may be difficult in small biopsies [82, 83]. Patients may be asymptomatic, present with a bleeding ulcer mimicking a primary gastric carcinoma (39 % of the cases), or with a submucosal tumor (51 % of the cases).

The most commonly observed error in the diagnosis of diffuse signet ring cell carcinoma occurs with metastatic lobular breast carcinoma, which has a propensity to metastasize and colonize the gastrointestinal tract as well as other

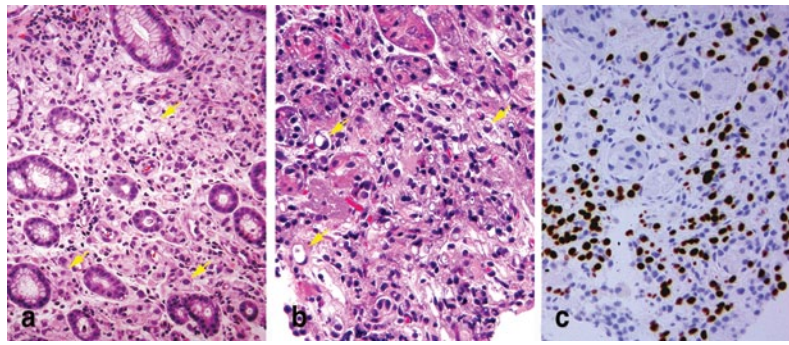

Fig. 4.8 Differential diagnosis of diffuse carcinoma in gastric biopsies. Primary diffuse gastric carcinoma (**a**) and metastatic breast lobular carcinoma to the stomach (**b**) share morphologic features (*Arrow*) and the distinction between them may sometimes be impossible. An immunostain for estrogen receptor is usually positive in classic lobular carcinoma (**c**)

hollow organs such as the uterus and the urinary bladder. Primary gastric diffuse signet ring cell carcinoma and lobular breast carcinoma share similar morphologic features and sometimes, the two neoplasms can be indistinguishable on the morphologic basis alone (Fig. 4.8a, b). Immunohistochemical studies can be helpful, since classic lobular breast carcinoma is usually immunoreactive to estrogen receptor (ER) (Fig. 4.8c), cytokeratin-7 (CK7), and mammaglobin; and a gastric primary carcinoma is immunoreactive for both CK7 and CK20, and should be negative for ER and mammaglobin.

Most importantly, a clinical history, even in the remote past, of breast carcinoma should prompt the appropriate work up to exclude a metastasis before the diagnosis of primary gastric diffuse signet ring cell carcinoma. Female patients with hereditary CDH1 mutation are at risk of developing both diffuse type gastric adenocarcinoma and lobular breast carcinoma, although the reported incidence of the latter is lower [45].

Gastrointestinal stromal tumor (GIST) can occur at any site of the GI tract; the stomach is one of the most common locations. When a GIST has epithelioid morphology, it can be difficult to distinguish from a poorly differentiated primary gastric carcinoma. Although subtle morphologic details may suggest the diagnosis of a GIST, such as intercellular myxoid stroma (Fig. 4.9a), a lack of cytokeratins immunoreactivity and positive reactivity to c-kit (CD117) confirms a diagnosis of GIST (Fig. 4.9b).

Other poorly differentiated malignant epithelial or epithelioid tumors, including seminoma (Fig. 4.9c), melanoma (Fig. 4.9d), and renal cell carcinoma, can metastasize to the stomach. Therefore, a poorly differentiated neoplasm in a gastric biopsy requires a thorough clinical and pathologic evacuation to exclude the possibility of a metastasis before the establishment of a primary gastric cancer. Among metastatic glandular/tubular carcinomas, pulmonary and pancreatic origins are more common than other primaries.

Biopsy Diagnosis of Early Gastric Cancer

Adenocarcinoma confined to the gastric mucosa (pathologic stage pT1a) or submucosa (pT1b) is defined as early gastric cancer (EGC) [7], and represents an early stage in tumor development. In Western series, EGC represents 15–20% of the newly diagnosed gastric cancers, whereas in Japan it accounts for more than 50% of the cases [2–5]. A higher prevalence of gastric cancer, more liberal use of upper endoscopy and chromoendoscopy, and differences in diagnostic criteria may explain the differences between Western and Japanese studies.

Most EGCs are typically located on the lesser curvature, around the angularis, and majority of them are well differentiated tubular or papillary

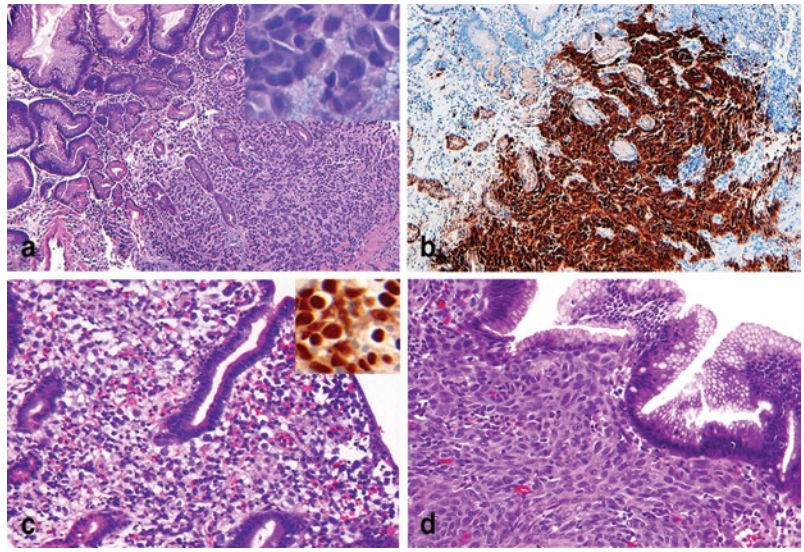

Fig. 4.9 Differential diagnosis of poorly differentiated epithelioid neoplasms in gastric biopsies. **a** Epithelioid gastrointestinal stromal tumor (GIST) involves gastric mucosa; the tumor cells exhibit intercellular myxoid stromal (*insert*) which is a subtle feature of GIST. **b** An immunostain of c-KIT (CD117) can confirm the diagnosis of GIST. **c** Metastatic seminoma involving gastric mucosa and an immunostain of octamer-binding transcription factor 4 (OCT4) (*insert*) is usually positive in tumor cells. **d** Metastatic melanoma involving gastric mucosa

variants [7]. These features create a challenging differential diagnosis between high-grade glandular dysplasia/carcinoma in situ (pTis) (Fig. 4.10a), and minimally invasive carcinoma (pT1a). The latter may present as either (1) individual cribriform glands with an associated expansile growth pattern (Fig. 4.10b) or (2) with nominal tumor invasion in the lamina propria (Fig. 4.10c); in both histologic prototypes, the tumor has progressed beyond the level of glandular dysplasia and met the diagnostic criteria of superficial gastric adenocarcinoma. When carcinoma invades through the muscularis mucosa, the tumor is staged as pT1b (Fig. 4.10d). Diffuse-type EGCs tend to exhibit greater width and depths of invasion and thus are less challenging to diagnose.

In some situations, well differentiated tubular or papillary adenocarcinomas may be present as detached fragments in a superficial biopsy. In the absence of stroma in a biopsy, the distinction between glandular dysplasia (pTis), genuine superficial carcinoma (pT1a), or invasive carcinoma in an exophytic mass is difficult to establish on the basis of microscopic features (Fig. 4.11). Nevertheless, correlations of endoscopic impressions and histologic findings can facilitate the accurate diagnosis.

Intraoperative Margin Assessment

Resection margins are among the strongest predictors of cancer-related mortality for gastric adenocarcinoma. An intraoperative consultation with a pathologist, including a frozen section of the specimen to microscopically assess the margin status, offers an opportunity to modify surgical management with the goal of achieving an R0 resection. The frozen section interpretation of the proximal margin deserves special attention since this is where most errors occur. In one study, the estimated overall diagnostic accuracy of frozen section at the proximal margin was 93 %, with a sensitivity of 67 %, a specificity of 100 %, a positive predictive value of 100 %, and a negative predictive value of 91 % [84]. Importantly, diffuse signet ring cell cancer constitute > 83 % of the false-negative readings.

When assessing the margin status, the specimen is opened to examine the location of the

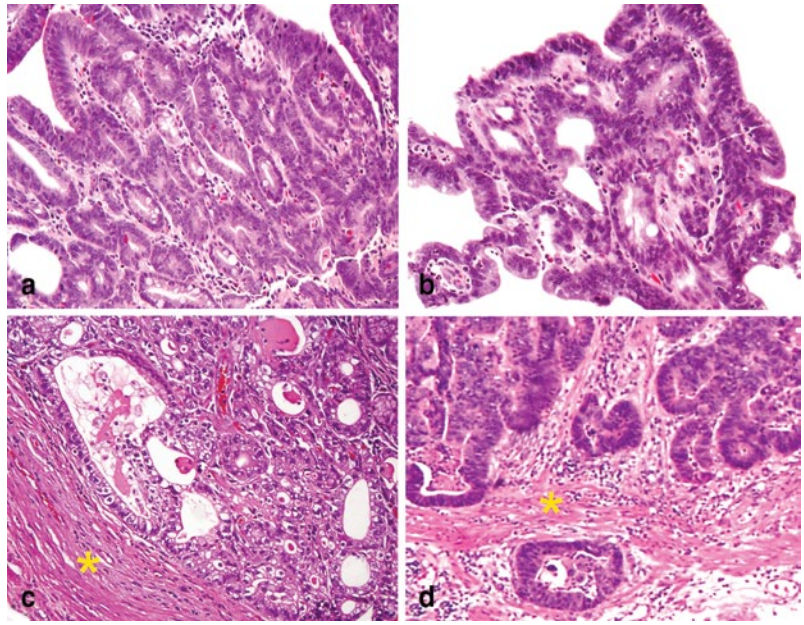

Fig. 4.10 Biopsy diagnosis of early gastric cancer. **a** High-grade glandular dysplasia with crowded glands in the superficial lamina propria is staged as in situ carcinoma (pTis). **b** An example of early gastric adenocarcinoma which exhibits expansile and complex glandular architecture, thus the lesion has progressed beyond high-grade dysplasia. Although stromal invasion cannot be assessed in this superficial biopsy, the tumor should be staged as pT1a. **c** Adenocarcinoma with extensive lamina propria invasion, but the tumor is confined to the mucosa without muscularis mucosae (marked by *) invasion and is staged as pT1a. **d** Adenocarcinoma has invaded thought the muscularis mucosae (marked by *) and into the superficial submucosa, and the tumor is staged as pT1b

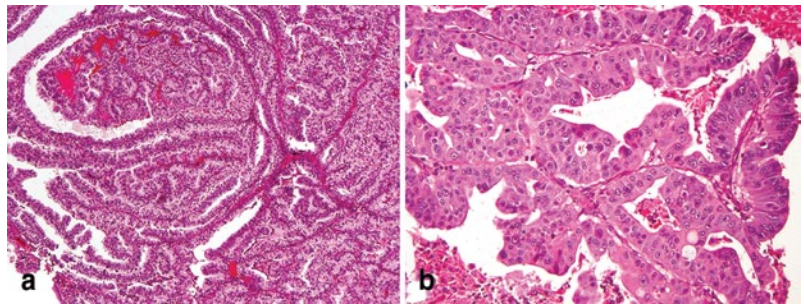

Fig. 4.11 Biopsy diagnosis of detached gastric carcinoma. **a** Papillary variant of gastric adenocarcinoma exhibits well differentiated morphologic and cytologic features with minimal intratumoral stroma. **b** A biopsy of papillary carcinoma may be indistinguishable from high-grade glandular dysplasia

tumor and its relationship to the resection margins. The decision as to where to take the frozen section is at the discretion of the pathologist based upon his/her judgment upon examination of the gross specimen. In the presence of a discrete lesion and gross margin clearance of more than 2 cm, a representative section at the site of the closest margin is adequate. When the tumor diffusely involves the entire stomach, particular in cases of diffuse signet ring cell subtype, it is necessary to submit the entire proximal and margin if this is surgically indicated. When the carci-

noma is present in the mucosal surface, the interpretation of a positive margin is straightforward. Oversight usually occurs when the cancer is present deep in the gastric wall as scattered malignant cells, particularly in cases of diffuse signet ring cell subtype. Therefore, explicit knowledge of the specific subtype of gastric carcinoma facilitates the evaluation of margin status at the time of intraoperative assessment (Fig. 4.12).

Pathologic Stage of Gastric Cancer

The American Joint Committee on Cancer Staging (AJCC) periodically updates their guidelines for staging cancer spread according to the size of the tumor (T-stage), amount of nodal metastasis (N-stage) and the presence or absence of extra-organ metastasis (M-stage). The most recent update occurred in 2010 (Table 4.3) [85].

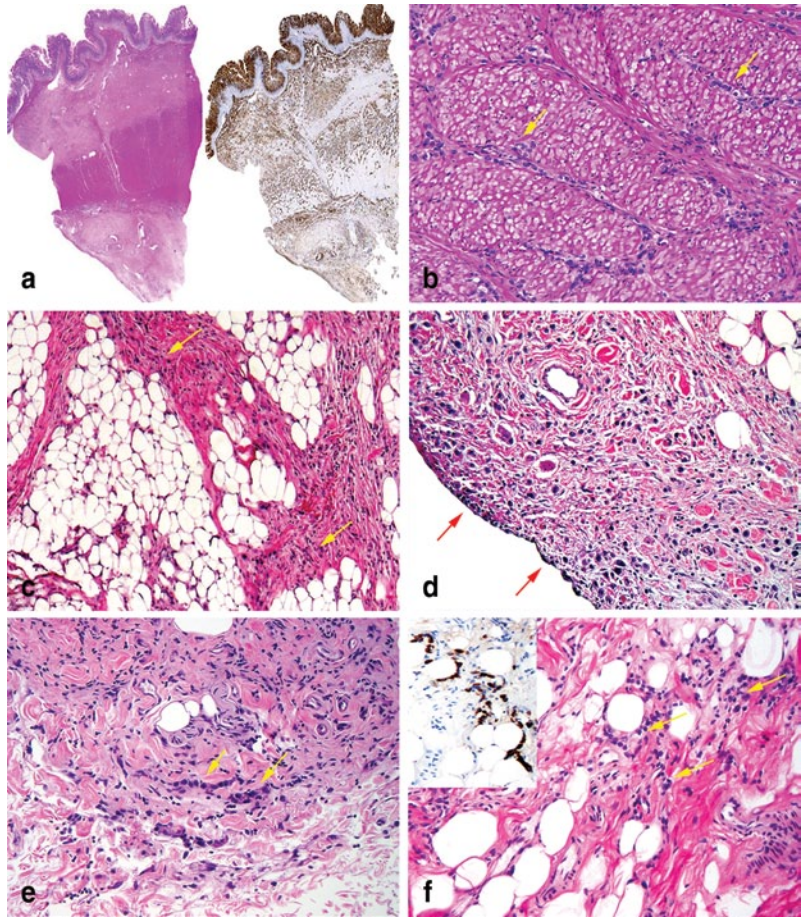

Fig. 4.12 Intraoperative diagnosis of margin status. **a** Diffuse type gastric adenocarcinoma causes thickened gastric wall (*left*) without histologic abnormalities at the mucosal surface. An immunostain of cytokeratin demonstrates transmural infiltration of tumor cells in the gastric wall (*right*). **b** The tumor cells infiltrate between muscular fibers (*arrows*). **c** The tumor cells infiltrates within fibrous septae in subserosal fat (*arrows*). **d** The tumor cells are commonly present at the serosal surface (*arrows*). **e, f** At intraoperative evaluation of the margin status, the tumor may be present in the deep gastric wall as scatted cluster or individual cells, which are better appreciated on an immunostain for cytokeratin

Table 4.3 Gastric cancer TNM staging [85]

Primary tumor (T)		Stage grouping			
TX	Primary tumor cannot be assessed	Stage 0	Tis	N0	M0
T0	No evidence of primary tumor	Stage IA	T1	N1	M0
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria (i.e., high grade dysplasia)	Stage IB	T2	N0	M0
T1	Tumor invades lamina propria (T1a), muscularis mucosae (T1a), or submucosa (T1b)		T1	N1	M0
T2	Tumor invades muscularis propria	Stage IIA	T3	N0	M0
T3	Tumor penetrates submucosal serosa without invasion of visceral peritoneum or adjacent structures		T2	N1	M0
T4	Tumor invades serosa (visceral peritoneum) (T4a) or adjacent structures (T4b)		T1	N2	M0
Regional Lymph Nodes (N)		Stage IIB	T4a	N0	M0
NX	Regional lymph node(s) cannot be assessed		T3	N1	M0
N0	No regional lymph node metastasis		T2	N2	M0
N1	Metastasis in 1 to 2 regional lymph nodes		T1	N3	M0
N2	Metastasis in 3 to 6 regional lymph nodes	Stage IIIA	T4a	N1	M0
N3	Metastasis in 7 or more regional lymph nodes		T3	N2	M0
Distal Metastasis (M)			T2	N3	M0
M0	No distant metastasis	Stage IIIB	T4b	N0	M0
M1	Distant metastasis		T4b	N1	M0
			T4a	N2	M0
			T3	N3	M0
		Stage IIIC	T4b	N2	M0
			T4b	N3	M0
			T4a	N3	M0
		Stage IV	Any T	Any N	M1

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Pathologic Assessment After Neoadjuvant Therapy

Although grading systems for tumor response have not been established, response of tumor to previous chemotherapy or radiation therapy should be reported. The assessment of pathological response to neoadjuvant therapy involves both the gross and the microscopic examination of the resected surgical specimen. At the microscopic level, a positive treatment-related effect is observed as abolition of the malignant epithelium and replacement by dense fibrosis or fibroinflammation. The pathologic response to treatment is determined by the amount of residual viable carcinoma in relation to areas of fibrosis or fibroinflammation within the gross lesion (Fig. 4.13). This relationship can be expressed as the inverse percentage of a favorable treatment response. Thus, a 100 % treatment response indicates fibrosis or fibroinflammation within an entire gross lesion without microscopic evidence of carcinoma,

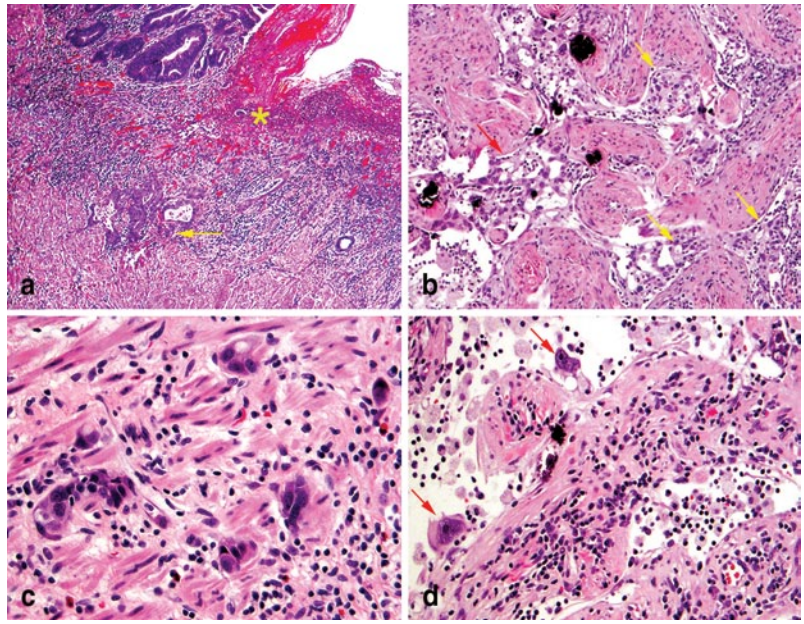

Fig. 4.13 Pathology assessment of gastric carcinoma post neoadjuvant therapy. **a** Gastric mucosa with surface ulceration and fibrin deposition (Marked by *) with clusters of residual carcinoma (*arrow*). **b** Although the carcinoma is mostly viable (*arrow*), the treatment associated changes are apparent which include inflammation, fibrosis, and dystrophic calcification (*dark spots*). **c** Moderate treatment effect with residual carcinoma preset as incomplete glands, small clusters, and individual cells. **d** Marked treatment response with near complete tumor regressions; the residual tumor cells are present as rare single cells (*arrows*)

while a 0 % response represents an entirely viable tumor in the absence of any fibrosis or fibroinflammation. The presence of viable tumor cells suggests incomplete response. Acellular mucin is regarded as a form of positive treatment response, not as viable tumor. The pathologic stage of the residual carcinoma is based on the deepest focus of viable malignant epithelium of the gastric wall. Positive lymph nodes are defined as having at least one focus of viable tumor cells in lymph nodes [86]. As an alternative, 3 category systems also provide good interobserver reproducibility (Table 4.4) [87].

Molecular Pathology of Gastric Carcinoma

Gastric adenocarcinoma develops as a result of an interaction between predisposing environmental conditions, genetic and epigenetic abnormalities, and mutations that affect oncogenes, tumor suppressor genes, and DNA mismatch repair genes [88–90]. The majority of gastric cancers are associated with an infectious etiology, including the *Helicobacter pylori* [91] and Epstein–Barr virus (EBV) [27]. The distribution of histological subtypes of the disease and the frequencies of *H. pylori* and EBV associated gastric cancer vary

Table 4.4 Grading system for tumor regression following administration of neoadjuvant therapy [87]

Description	Tumor regression grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

across the world [92]. A minority of gastric cancer cases are associated with germline mutation in E-cadherin (CDH1) [93] or DNA mismatch repair genes (Lynch syndrome) [94], whereas sporadic mismatch repair-deficient associated gastric cancers have epigenetic silencing of MLH1 in the context of a CpG island methylator phenotype (CIMP) [95].

Lauren's phenotypic classification of gastric cancer into intestinal or diffuse subtypes has been valuable in providing the basis for providing a genotypic classification of gastric carcinoma. Previously, molecular profiling of gastric cancer has been performed using gene expression or DNA sequencing [72, 96–98]. However, these studies have not led to a pathobiology classification scheme of the disease.

Recently, The Cancer Genome Atlas (TCGA) has developed a robust molecular classification of gastric cancer and identified dysregulated pathways and some candidate driver mutations of distinct classes of gastric cancer [29]. The TCGA studies have characterized four major genomic subtypes of gastric cancer: (1) EBV-infected cancer, (2) MSI cancer, (3) genomically stable cancer, and (4) chromosomally unstable cancer. These molecular subtypes reveal prominent genomic features, and provide a guide to targetable agents. This work will facilitate the development of clinical trials to explore therapies in defined sets of patients, ultimately improving survival from this deadly disease [29].

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