
Pathologic Features of Esophageal and Gastric Malignancies

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Abstract

Esophageal and gastric carcinomas affect millions of individuals worldwide, placing a considerable burden on society. Unfortunately, preventative medicine falls short as screening methods for the upper gastrointestinal tract lack the ability to detect early onset disease. The overwhelming majority of cases present after symptoms appear when individuals have advanced disease with a poor prognosis. Further complicating matters, the anatomic location of these neoplasms engenders rapid tumor progression, which repeatedly thwarts successful surgical treatment. This chapter will focus on the pathological features of malignant neoplasms of the esophagus and stomach.

Keywords

Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Adenosquamous carcinoma · Adenoid cystic carcinoma · Gastric adenocarcinoma · *Helicobacter pylori*

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1 Esophagus

Esophageal cancer affects more than 450,000 people worldwide and currently ranks sixth among cancer-related mortality [45]. The prognosis is poor as many patients present with locally incurable or metastatic disease. The incidences rates vary dramatically worldwide, which can be attributed to demographic and socioeconomic factors. Although the vast majority of esophageal neoplasms arise from the epithelial layer and include squamous cell carcinoma (SCC) and adenocarcinoma (AC), a subset of neuroendocrine and soft tissue tumors can also occur in the esophagus (Table 1). Several tasks are presented to the surgical pathologist when dealing with esophageal carcinoma: rendering a diagnosis, classifying the histological type, and assessing prognostic factors. Therefore, we will focus on these topics as we discuss various esophageal neoplasms.

1.1 Squamous Cell Carcinoma

Worldwide, squamous cell carcinoma (SCC) is the most common variant of esophageal carcinoma. The highest incidence rates are seen in underdeveloped settings, particularly in parts of Iran, China, and Africa. In contrast, western countries have seen a considerable decrease in squamous lesions, with an accompanying increase in adenocarcinoma [13]. This demographic discrepancy is not completely understood, and possibly attributed to varying etiological factors as no single causative agent has been identified. Males are affected more commonly than females, and incidence peaks in the sixth decade [6]. The pathogenesis remains incompletely defined, but thought to be a

Table 1 Classification of esophageal tumors

Epithelial tumors	Premalignant Squamous Glandular	Malignant Squamous cell carcinoma Adenocarcinoma Adenoid cystic carcinoma Adenosquamous carcinoma Basaloid squamous cell carcinoma Mucoepidermoid carcinoma Verrucous (squamous) carcinoma Spindle cell (squamous) carcinoma Undifferentiated carcinoma
Mesenchymal tumors	Benign Granular cell tumor Hemangioma Leiomyoma Lipoma	Malignant Kaposi sarcoma Gastrointestinal stromal tumor Leiomyosarcoma Melanoma Rhabdomyosarcoma Synovial sarcoma
Neuroendocrine tumors	Neuroendocrine tumors (NET)	Neuroendocrine carcinoma Mixed adenoneuroendocrine carcinoma
Lymphoma		

multistep process stemming from precancerous changes in the squamous epithelium. It was once believed that esophagitis was a precursor for SCC as prospective studies in high-risk areas have documented a dysplasia-to-carcinoma progression [47, 59]. Risk factors include tobacco, alcohol, poverty, dietary N-nitroso compounds, lack of dietary fruits and vegetables, and poor nutritional status. A history of smoking and alcohol use account for the majority of cases in Europe and North America, however the importance of these factors is substantially different in developing nations. The current literature remains inconclusive on whether human papilloma virus (HPV) is a prominent carcinogen in esophageal SCC [36].

1.1.1 Clinical Features

The most common symptoms of advanced lesions are dysphagia and weight loss. Pain occurs in the epigastrium or retrosternal area. Superficial lesions have vague and nonspecific symptoms, sometimes associated with a tingling sensation or persistent cough. The majority of SCCs are located in the lower two-thirds of the esophagus, followed by the upper segment. The lesion presents as either a depression or elevation of the mucosa.

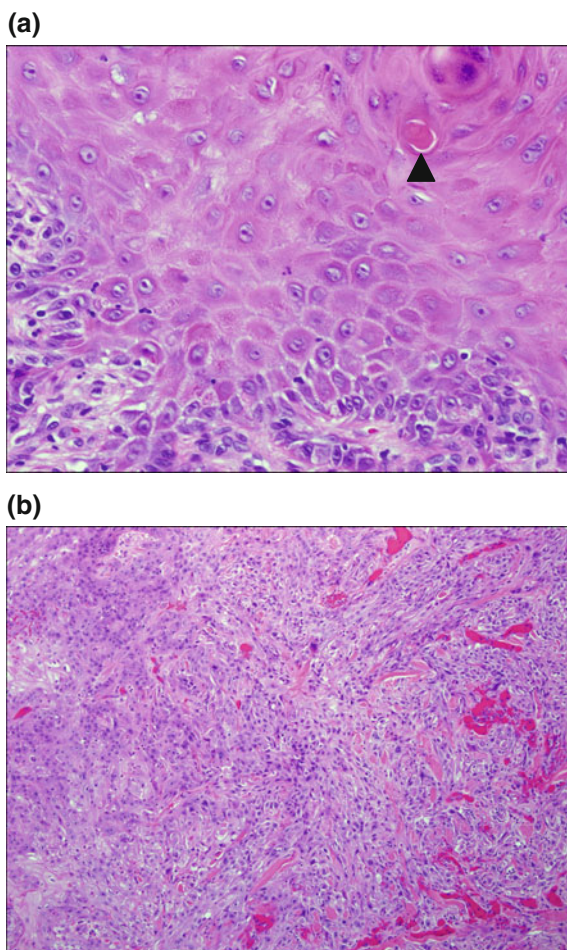
1.1.2 Gross Pathology

Superficial lesions more frequently appear as plaques or small ulcers, while advanced lesions are often deep ulcerations or fungating masses. However, features do overlap and depth of invasion is not always clearly discernible on endoscopy. Misinterpreting an infiltrative luminal narrowing for a benign stricture is a common pitfall. Alternatively, benign esophagitis presents as an extensive, diffusely ulcerated, flat lesion similar to superficial-type SCC. Imaging techniques like three-dimensional CT, endoscopic ultrasound, or 18-fluoro-2deoxyglucose-positron emission tomography (PET) can effectively demonstrate certain staging parameters. While preoperative imaging and endoscopy are nearly diagnostic, a biopsy is required for confirmation and accurate histological classification, no matter how high the index of clinical suspicion.

1.1.3 Microscopic Pathology

Dysplasia evolves through a spectrum, where changes begin at the base of the epithelium (low-grade) and progress to the surface (high-grade). The cytological features include large, dark staining nuclei with coarse chromatin (hyperchromasia), variation in nuclear size and shape (pleomorphism), loss of epithelial order, and mitotic activity above the basal layer. Atypical cells trailing off into the lamina propria or deep aberrant keratinization are potentially worrisome signs of invasion. Squamous cell carcinoma is composed of polygonal cells with abundant eosinophilic (pink) cytoplasm, intercellular bridges (tight junctions between neighboring cells), and variable amounts of keratinization. The nucleus is large, dark, and contains a prominent nucleolus. Tumor grading evaluates cellular differentiation, the degree of atypia, and mitotic activity. Generally, tumor grading is a means to predict the tumors biological behavior. A low-grade SCC has a lesser degree of atypia as the cells are well-differentiated (Grade 1), thus resembling native squamous epithelium (Fig. 1a). High-grade SCC (Grade 3) has severe atypia and is

Fig. 1 Squamous cell carcinoma (SCC). **a** In well-differentiated SCC (Grade 1), the tumor cells have abundant pink cytoplasm and keratin formation is evident (*arrowhead*). **b** In poorly-differentiated SCC, the tumor cells are more difficult to appreciate as being squamous in origin and invade as single cells or small clusters of cells



inherently aggressive (Fig. 1b). The frequency of lymphatic and blood vessel invasion increases with increasing depth of invasion [52]. Immunohistochemistry is used judiciously, as most diagnoses can be made solely on histological grounds, however, squamous cell carcinomas are typically positive for cytokeratin 5/6, p63, and p40 by immunohistochemistry. There are currently three histological variants of SCC recognized:

Verrucous Carcinoma: Verrucous carcinoma grossly has a distinctive wart-like appearance (Fig. 2). It is considered a low-grade tumor with pushing borders (bulbous growth of neoplastic cells which push normal tissue aside). The behavior is defined by slow growth with local spread and infrequent metastases. If not properly excised, recurrence tends to be local. Endoscopic correlation is essential as superficial biopsies can underdiagnose the low-grade histology [37].

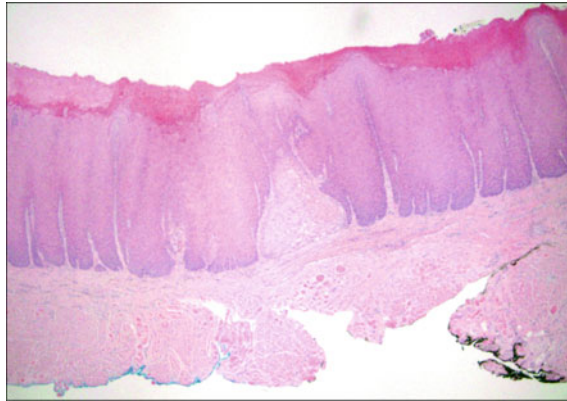
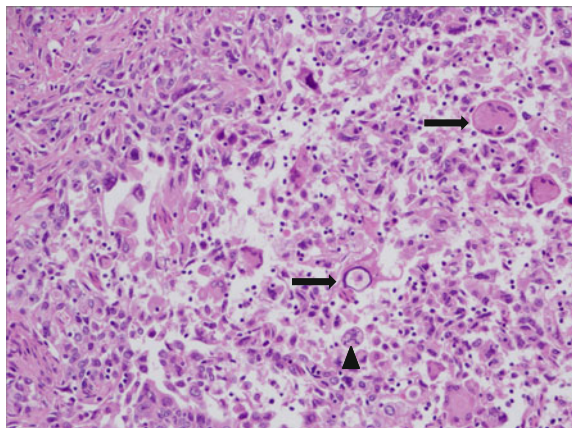


Fig. 2 Verrucous carcinoma. This low-power photomicrograph reveals well-differentiated hyperplastic squamous epithelium with orderly maturation, hyperkeratinization, and broad “finger-like” projections with a typical downward, pushing border characteristic of this entity

Fig. 3 Spindle cell (squamous) carcinoma. The tumor cells have lost their epithelioid morphology and appear more spindled with bizarre, pleomorphic nuclei (arrows) and atypical mitoses (arrowhead)



Spindle Cell (Squamous) Carcinoma: The key diagnostic feature is biphasic morphology; well- to moderately differentiated squamous cells admixed with sarcoma-like spindle cells (Fig. 3). The spindle cell component is usually high grade with increased pleomorphism. Overall the prognosis is favorable because the tumor tends to grow outward in a polypoid fashion [48]. Immunohistochemical staining for pancytokeratin can be used to highlight the epithelial differentiation of the neoplastic cells.

Basaloid Squamous Cell Carcinoma: Basaloid squamous cell carcinoma is distinctive for its proximal location. Characterized by large, rounded nests of small blue cells with peripheral palisading and central necrosis (Fig. 4). These tumors tend to be deeply invasive with widespread metastasis at the time of diagnosis. Patients demonstrate poor cancer-related and disease-free survival rates [51].

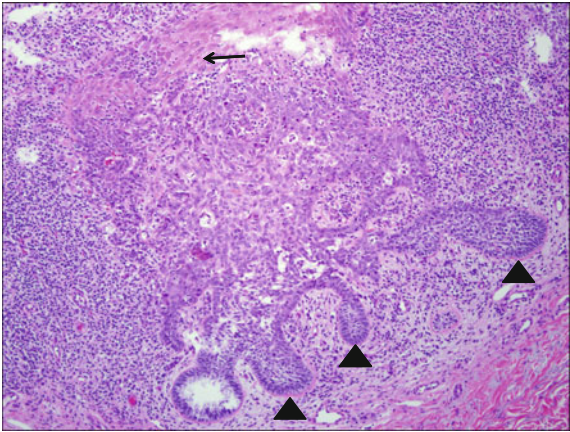


Fig. 4 Basaloid squamous cell carcinoma. Both squamous and basaloid components are present within this tumor. Basaloid cells are *blue* cells with peripheral palisading row of elongated nuclei parallel to one another) (*arrowhead*). The squamous cell component reveals a densely *pink* cytoplasm (*arrow*)

1.1.4 Prognostication

The TNM system used by the American Joint Commission on Cancer (AJCC) is the most widely accepted staging system [14, 56, 61]. The extent of tumor spread is determined by specific staging parameters (TNM classification) and the type of

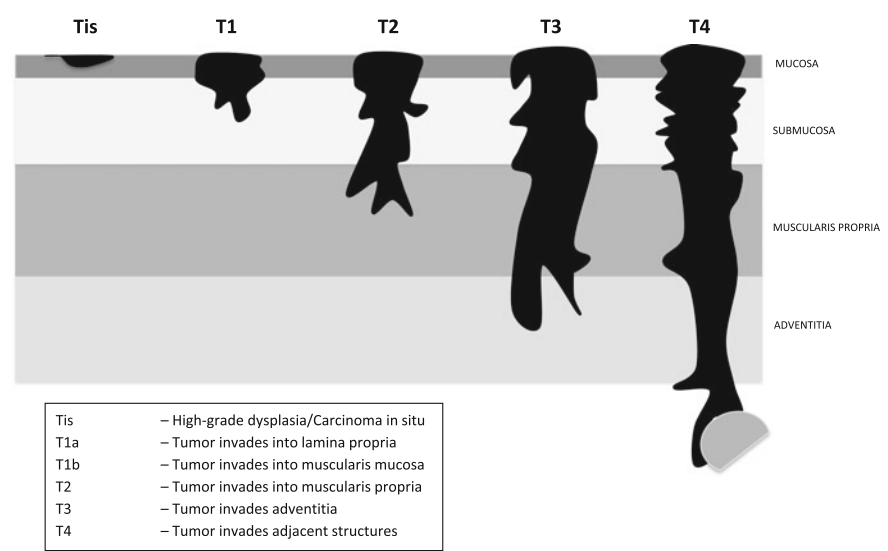


Fig. 5 Tumor staging based on depth of invasion. The single most important parameter, in terms of prognostics, is depth of invasion. Lymphatics originate within the lamina propria and invasion into the lamina propria or beyond results in a T1 stage or higher. Invasion of tumor cells beyond the adventitia with involvement of other structures is a T4 stage

treatment a patient receives is dependent on the extent of disease. The best predictor of outcome and treatment response is the depth of invasion (T-stage), and therefore demands an accurate microscopic measurement. Like all segments of the gastrointestinal tract, the esophagus can be divided into four distinct histological layers: mucosa, submucosa, muscularis propria, and serosa (Fig. 5). The mucosa consists of a protective stratified squamous epithelium and is contained by a basement membrane. Any dysplastic process contained within the mucosa is defined as high-grade dysplasia or carcinoma in situ (Tis). Any neoplastic process invading beyond the basement membrane of the mucosa into deeper layers will be upstaged from Tis into T1 through T4. The reason for this is because the lymphatic system originates in the lamina propria, where neoplastic cells have the potential to metastasize [52, 58]. At the time of diagnosis, most patients present with advanced lesions invading into the muscularis propria, heralding a grim prognosis. The 5-year survival rate amidst tumors restricted to the esophageal wall is roughly 50 %, while penetration into or beyond the adventitia is associated with a worse outcome. Roughly 60 % of patients demonstrate lymph node involvement as the frequency of lymph node involvement is related to depth of invasion (40 % in submucosal extension compared to 5 % for intramucosal lesions) [1]. In addition to traditional features such as invasion and lymph node involvement, tumor grading is implemented to help clinically stratify patients and further predict outcome. Although controversy exists as to whether tumor grading significantly influences survival, over the last decade the American Joint Committee on Cancer (AJCC) has incorporated histology as a parameter for clinical staging of esophageal carcinoma [14, 39].

1.1.5 Molecular Pathology

The loss of several tumor suppressor genes is associated with SCC, of which mutation in the TP53 gene is an early event sometimes detectable in high-grade dysplasia [39]. Other molecular factors include: alterations in p16/INK4a [64], amplification of cyclin D1 [26], and inactivation of CDKN2A [53]. TP53 is mutated in 35–80 % of SCCs [38], and its nuclear accumulation has shown to be a negative prognostic indicator [54].

1.2 Esophageal Adenocarcinoma

Adenocarcinoma (AC) differs from squamous cell carcinoma based on histology, but also on various epidemiological characteristics. For the past three decades, the occurrence of adenocarcinoma has increased dramatically [7, 46]. This trend has been particularly dominant in Western countries, like the United States and United Kingdom, where rates have exceeded that of squamous cell carcinoma. Epidemiological factors of adenocarcinoma overlap with Barrett esophagus (BE), as the incidence of BE has increased in tandem with the increasing rates of AC [62].

At the gastroesophageal junction, complications of chronic gastroesophageal reflux disease (GERD) result in the development of intestinal metaplasia. That is, after repeat bouts of injury, the healing process transforms squamous epithelium

into a mucin filled, columnar glandular-type epithelium with goblet cells (Barrett esophagus). Over time, the columnar epithelium can progress in a stepwise fashion through dysplasia and eventually develop into invasive carcinoma. Although familial association has been reported, population-based studies have shown rapid changes in incidence rates in different populations over short periods of time, likely indicating limited hereditary influence [33]. Barrett esophagus is the single most important risk factor in developing esophageal adenocarcinoma [29]. Obesity appears to be associated with increased risk and smoking appears to have a negative impact.

1.2.1 Clinical Features

Clinical symptoms of esophageal adenocarcinoma are generally associated with dysphasia, weight loss, and abdominal pain. In contrast to squamous cell carcinoma, AC invariably arises distally and therefore tumor location is not incorporated into the staging. Since esophageal adenocarcinoma can involve the gastroesophageal junction (GEJ) and carcinoma of proximal stomach can invade the distal esophagus, distinguishing between these two entities is challenging [57]. Accurate anatomical localization is imperative for proper classification and staging [27]. Tumors with an epicenter at or above the gastroesophageal junction (GEJ) or within the proximal 5 cm of stomach with extension into GEJ are staged and classified as esophageal tumors [55]. Endoscopists should attempt to identify the most proximal gastric folds or the columnar (Barrett) epithelium to establish the GEJ. Large tumors can obliterate evidence of adjacent Barrett mucosa, concealing the esophageal origin.

1.2.2 Gross Pathology

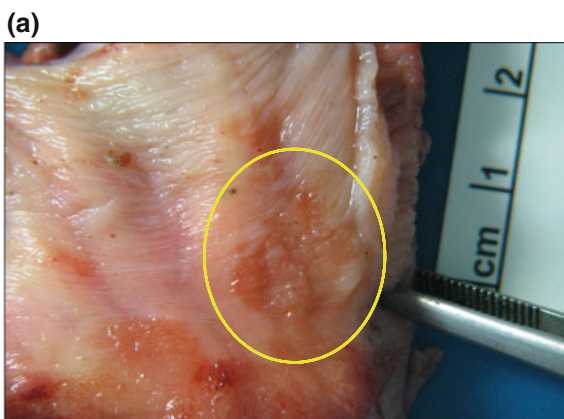
Grossly, adenocarcinoma looks similar to squamous cell carcinoma, and can present as either flat, irregular plaques (Fig. 6a), polypoid lesions (Fig. 6b), or an ulcerated, fungating mass (Fig. 6c). At early stages, macroscopic findings are often subtle, with the salmon pink mucosa of Barrett esophagus (columnar epithelium with goblet cells) located adjacent to the tumor. High-grade dysplasia is often not visibly apparent and requires tissue sampling [15]. Even invasion is difficult to identify grossly; often being flat and occasionally arising independently from Barrett mucosa. Determining invasion on endoscopy (without the assistance of ultrasound) can be unreliable.

1.2.3 Microscopic Pathology

In general, when dysplasia develops in Barrett esophagus, glands acquire a dark blue hue as cells lose mucin, become more crowded, and develop enlarged, hyperchromatic nuclei. These features should extend from the base of the glands up to the luminal surface. Unique in low-grade dysplasia, the crypt architecture is preserved with minimal distortion, containing cells with elongated, “pencil-shaped” nuclei limited to the basal portion of the cytoplasm. In high-grade dysplasia, cytological atypia progresses with increased nuclear pleomorphism, high nuclear-to-cytoplasmic ratio, frequent mitoses, loss of nuclear polarity and increased glandular complexity (back-to-back glands, cribriform/papillary patterns) (Fig. 7).

Fig. 6 Macroscopic appearance of esophageal adenocarcinomas.

a Superficial lesions appear as plaque-like areas (*yellow circle*) with punctate ulceration and erythematous mucosa. In more advanced lesions, the tumor can appear as a polypoid mass (**b**) or fungating lesion (**c**)



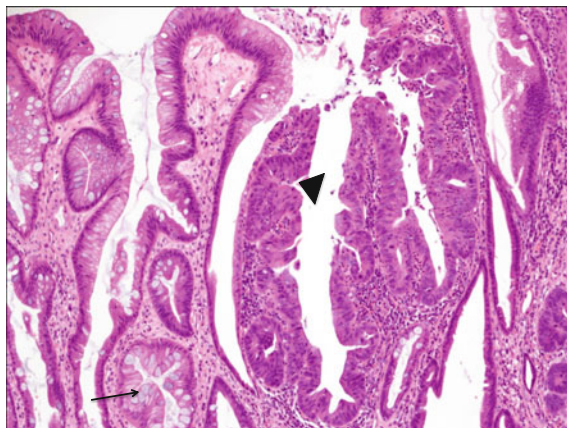


Fig. 7 Barrett esophagus. **a** The presence of mucinous, columnar epithelium with readily identified goblet cells (*arrow*) within the squamous mucosa of the esophagus is diagnostic of Barrett esophagus (BE). **b** Within the area of BE, there is increased hyperchromasia, loss of mucin, increased nuclear-to-cytoplasmic ratio and loss of polarity, characteristic of high-grade dysplasia (*arrowhead*)

With invasion, the border of the basement membrane appears ragged with single cells streaming off into the lamina propria. Tumor grading (well, moderately, or poorly-differentiated) classifies the tumor according to proportion of glandular formation. Well-differentiated tumors are composed of irregular glands with cuboidal–columnar epithelium (Fig. 8a). The nuclei contain coarse chromatin with prominent nucleoli. In moderately-differentiated carcinomas, there will be less glandular structures admixed with more complex architecture, composed of irregular cell clusters, nuclear stratification, and cribriform pattern (Fig. 8b). Glandular structures are scarcely visible in poorly-differentiated carcinomas, defined by bizarre pleomorphic cells arranged in sheets or scattered cells within a desmoplastic stroma (Fig. 8c). In small biopsies of well-differentiated tumors, the invasion is not striking and poses difficulties in diagnosis. If present, desmoplasia can help separate high-grade dysplasia from invasive carcinoma. Post-neoadjuvant therapy specimens may demonstrate extensive treatment effect, which consists of highly degenerated neoplastic cells within pools of acellular mucin (Fig. 9).

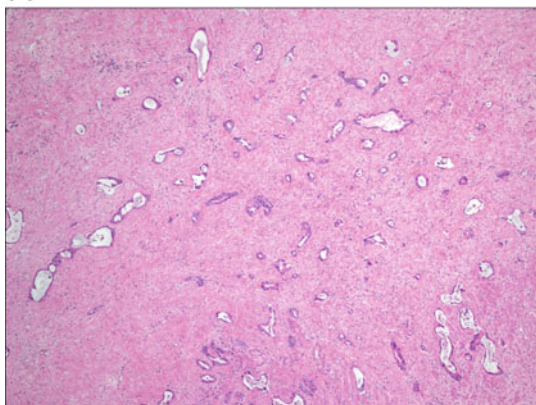
1.2.4 Prognostication

Although adenocarcinoma and squamous cell carcinoma differ in a number of features, including location, predisposing factors, and tumor biology, they share the same poor prognosis. Tumor stage is the most important parameter in determining survival [58]. Patients with tumors limited to the mucosa have a superior 5-year survival rate (85 %) than patients with muscularis propria involvement [49]. Unfortunately, by the time symptoms appear, most tumors have already reached advanced stages, with invasion into the esophageal wall noted in 60–80 % of cases and nodal involvement in up to 30 % of cases [19]. Neoadjuvant therapy is often

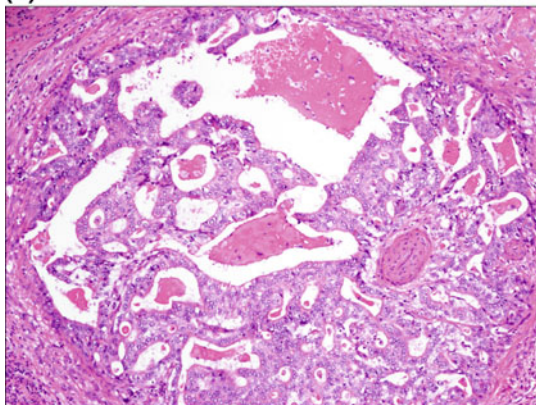
Fig. 8 Morphologic spectrum of esophageal adenocarcinoma.

a Infiltrating, well-differentiated adenocarcinoma demonstrates glands (tubular structures) within the muscularis propria, **b** “punched-out,” colander-like holes in a cribriform pattern in a moderately-differentiated tumor, and **c** solid sheet of single, poorly-differentiated tumor cells undermining the squamous mucosa

(a)



(b)



(c)

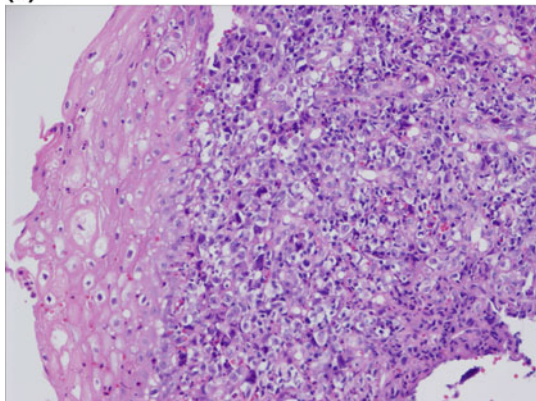
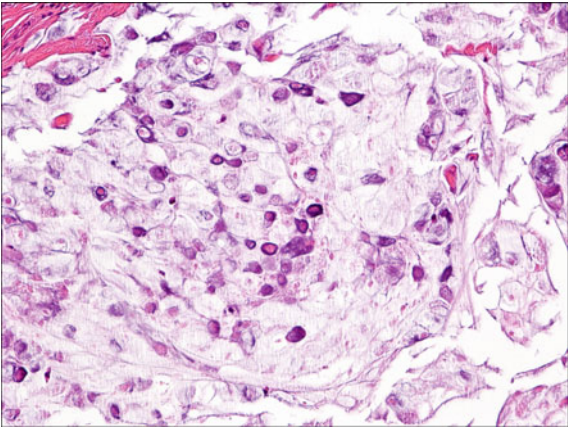


Fig. 9 Treatment effect. Following neoadjuvant treatment, there can be abundant collections of acellular mucin containing areas of calcification and rare, markedly degenerated, non-viable tumor cells



provided for advanced-stage tumors and the extent of residual carcinoma found in the resection specimen after therapy is a predictor of patient outcome [63]. Complete regression (0 % residual tumor remaining) reflects a positive tumor response to pre-operative treatment, and is recognized as a positive prognostic factor [3]. Modification of the AJCC TNM staging system resulted in separating squamous cell carcinoma from adenocarcinoma and both incorporate histological grade as a separate prognostic category [14]. Histological grading for AC carries a different weight in determining prognostic groups such that a poorly-differentiated (Grade 3) adenocarcinoma will be placed under the same prognostic grouping as a well- or moderately-differentiated squamous cell carcinoma (Table 2).

Table 2 The prognostic grouping of esophageal carcinomas

	Group	T	N	M	Grade	Location
Adenocarcinoma	IA	1	0	0	1–2	
	IB	1	0	0	3	
		2	0	0	1–2	
	IIA	2	0	0	3	
	IIB	3	0	0	Any	
		1–2	1	0	Any	
Squamous cell carcinoma	IA	1	0	0	1	Any
	IB	1	0	0	2, 3	Any
		2, 3	0	0	1	Lower
	IIA	2	0	0	1	Upper/middle
		2, 3	0	0	2, 3	Lower
	IIB	2–3	0	0	2,3	Upper/middle
		1–2	1	0	Any	Any

1.2.5 Molecular Pathology

Multiple genetic alterations involving tumor suppressor genes, oncogenes, and growth factor receptors play a role in cancer progression. Mutations or overexpression of TP53 occur as dysplasia progresses from low-grade to high-grade dysplasia and onto carcinoma [18, 25]. Allelic loss or epigenetic silencing by promoter methylation of cyclin dependent kinase inhibitor (CDKN2A/p16) has been demonstrated to be an early event in tumorigenesis [40]. Additional genetic changes include amplification of *c*-ERB-B2 [32] and cyclin D1 [2], and upregulation of COX2 [8] have been identified. Increased epithelial NF- κ B expression insinuates that inflammation is a likely contributing factor [24]. Several molecular markers are associated with a negative clinical outcome, including DNA aneuploidy, TP53 mutations, ERB-B2 amplification, and expression of COX2 or NF- κ B [23, 32].

1.3 Other Esophageal Carcinomas

1.3.1 Adenosquamous Carcinoma

These tumors contain mixed element of adenocarcinoma and squamous cell carcinoma, which are clearly demarcated within the lesion (Fig. 10). The histological mixture is diagnostically insignificant and prognosis is similar to typical squamous cell carcinoma.

1.3.2 Mucoepidermoid Carcinoma

A rare tumor derived from submucosal glands, displaying more intimately admixed elements of squamous cells, mucus secreting cells, and intermediate cells, which morphologically falls in between the other two cells types (Fig. 11).

1.3.3 Adenoid Cystic Carcinoma

Also an infrequent variant, believed to arise like mucoepidermoid carcinoma, from esophageal glands. The tumor is composed of small, bland, myoepithelial cells with

Fig. 10 Adenosquamous carcinoma. This tumor contains tumor cells with abundant pink cytoplasm characteristic of squamous cell carcinoma (*arrowheads*), along with areas that have the gland formation seen in adenocarcinoma (*arrows*)

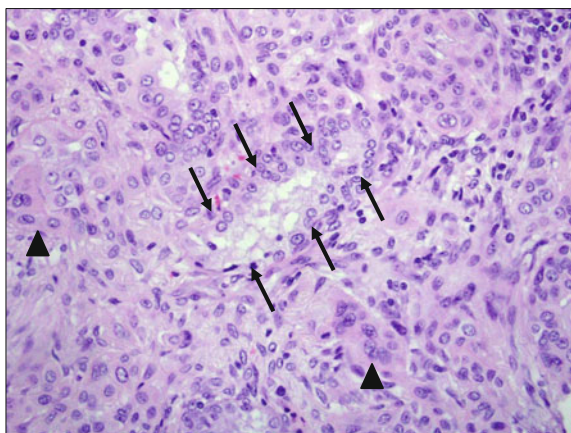


Fig. 11 Mucoepidermoid carcinoma. The tumor consists of cords or clusters of mucous (*arrows*), squamous cells (*arrowhead*), and intermediate cells, and often lacks high-grade atypia

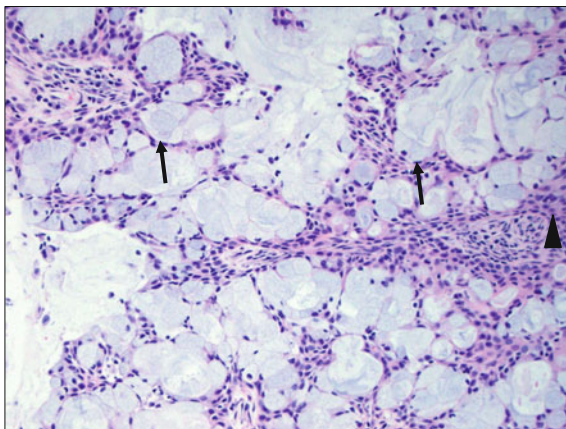
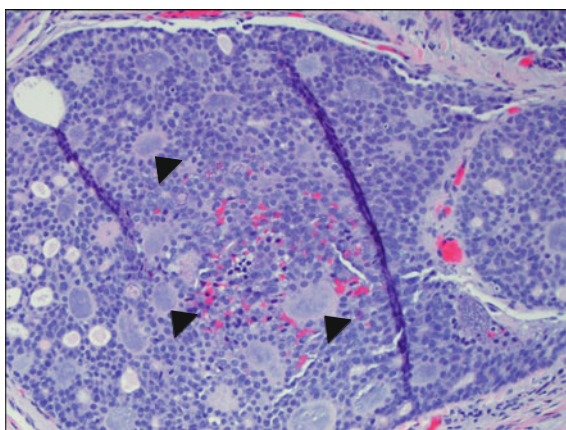


Fig. 12 Adenoid cystic carcinoma. The tumor is composed of small, bland cells with scant cytoplasm and the characteristic “punched-out,” cribriform pattern with mucus and basement membrane material within the center (*arrowheads*)



scant cytoplasm, dark compact angulated nuclei surrounding pseudoglandular spaces containing excess basement membrane material and mucin (Fig. 12). The principle diagnostic challenge is to distinguish this tumor from basaloid squamous cell carcinoma. Both adenoid cystic and mucoepidermoid carcinoma have a favorable prognosis compared to squamous carcinomas [41].

2 Stomach

There are numerous benign and malignant primary neoplasms that occur in the stomach arising from a multitude of precursor cells. Overwhelmingly, the majority of malignant tumors in the stomach are of epithelial origin (carcinomas), but

various other tumors of lymphoid, mesenchymal, and neuroendocrine differentiation may also arise in this location. As a group, primary gastric malignancies comprise a wide spectrum of morphology, histopathology, clinical behavior, and genetic makeup; an evolving understanding of the pathophysiology and genetic underpinnings of these lesions is necessary to guide new treatments and most effectively manage patients with these conditions.

3 Gastric Adenocarcinoma

Gastric adenocarcinoma is the fourth most common malignancy worldwide, with an incidence that varies widely with regard to geography. Although it was the leading cause of cancer-related mortality worldwide until the 1990s, primary gastric adenocarcinoma has become relatively rarer in many western countries with a rate that continues to decrease [4]. This decline has been attributed to decreased prevalence of risk factors, such as *Helicobacter pylori* infection and tobacco use [16]. However, there are still regions in which gastric adenocarcinoma is significantly more prevalent, such as Eastern Asia, South America, and Eastern Europe. There is also a correlation between geographic incidence and the location of the tumor in relation to gastric anatomy (i.e., centered at the gastric cardia vs. antrum/pyloris). Generally, the incidence of gastric tumors occurring in the cardia is higher in “low-incidence” regions such as North America, while the opposite is true of antral/pyloric tumors [28].

3.1 Pathogenesis of Gastric Carcinoma

The pathogenesis of gastric adenocarcinoma is closely related to several environmental risk factors. One notable risk factor is infection by the Gram-negative spirochete *Helicobacter pylori*. International epidemiologic studies indicate that the incidence of gastric cancer is proportional to the *H. pylori* infection rate within a given country, that falling rates of *H. pylori* infection coincide with a drop in the incidence of gastric adenocarcinoma [28], and infection with *H. pylori* confers at least a sixfold higher risk of gastric carcinoma than that of the general population [21]. It is well known that chronic inflammation serves an etiological role in many cancers [43], and the chronic gastritis that results from *H. pylori* infection has been cited as precursor to gastric adenocarcinoma. Additional proposed pathways of carcinogenesis by *H. pylori* include interference with apoptosis and the cell cycle, alteration of intercellular signaling, disruption of intercellular adhesive processes, and activation of proliferative intracellular signaling pathways, among others [42]. In addition to infection, other risk factors for gastric adenocarcinoma include smoking, prior gastric surgery, dietary factors (high salt intake, diets low in fruits and vegetables, high nitrite intake), ionizing radiation, and pernicious anemia/autoimmune gastritis [17]. Genetic and hereditary factors are also implicated in some types of gastric carcinoma; generally speaking, solid tumors with tubular architecture (intestinal-type carcinomas) are more related to environmental

risk factors while poorly circumscribed, widely infiltrative (diffuse type) carcinomas are more likely to be associated with genetic derangements [22]. The classification and molecular features of gastric carcinomas are discussed later in this chapter.

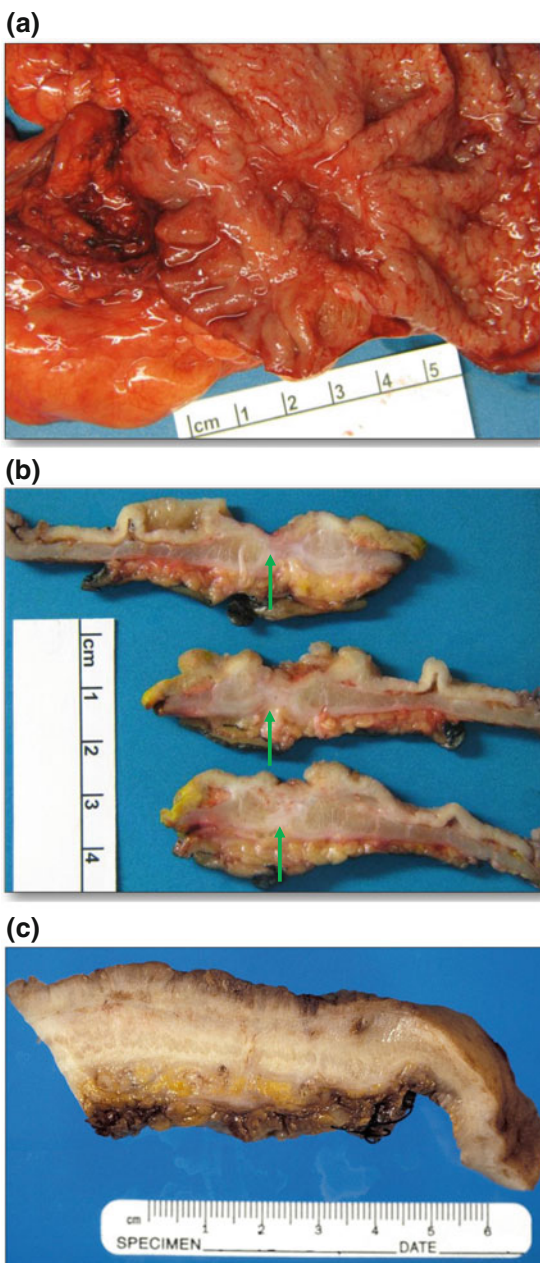
3.2 Gross Pathology

Gastric adenocarcinomas exhibit a wide spectrum of macroscopic morphology, ranging from grossly exophytic lesions to subtle widely infiltrative lesions. Gastric carcinomas may be macroscopically separated into early and advanced carcinomas. Early gastric carcinomas are tumors of any size and lymph node status which invade no deeper than the submucosa. Most early carcinomas range from 2 to 5 cm in greatest dimension [22]. The Paris system, proposed in 2002, designates early carcinomas as type 0 and further subcategorizes these lesions into types 0-I (polypoid), type 0-II (superficial), and type 0-III (excavated) according to their macroscopic architecture. These categories are further subclassified as shown in Table 3. Advanced carcinomas—those that invade deeper than the submucosa- are categorized into types I-IV according to macroscopic architectural features (the Borrmann Pathologic Classification of Gastric Cancer). Type I cancers (polypoid) are exophytic tumors which are dome-shaped and are usually attached to the surrounding stomach mucosa via a wide base. Polypoid tumors may range from having a relatively smooth overlying mucosa to more complex architecture featuring lobulation or irregular excrescences. Type II (ulcerated, circumscribed) carcinomas have a well-demarcated border which may be elevated or rolled, and there is often some degree of central ulceration. This type may feature irregular mounds and projections of the mucosa and is sometimes described macroscopically as fungiform/fungating. Type III (ulcerated, infiltrative) tumors are similar to type II in that central ulceration is a prominent feature, but these cancers demonstrate poor demarcation macroscopically and it is often difficult to grossly identify the extent of the lesion (Fig. 13a and b). Finally, type IV (infiltrative, non-ulcerative) tumors are

Table 3 Paris and Borrmann endoscopic classifications for gastric adenocarcinoma

Early carcinomas (Paris)	Type 0
	0-I: polypoid
	0-Ip: pedunculated
	0-Is: sessile
	0-II: superficial
	0-IIa: elevated
	0-IIb: flat
	0-IIc: depressed
	0-III: excavated
Advanced carcinomas (Borrmann)	Type I: polypoid
	Type II: ulcerated, circumscribed
	Type III: ulcerated, infiltrative
	Type IV: infiltrative, non-ulcerative

Fig. 13 Macroscopic appearance of gastric adenocarcinoma. **a** Tumor within the antrum exhibits central ulceration and heaped-up, poorly defined mucosal borders. **b** Sectioning of the tumor reveals infiltration into the muscularis propria but without extension to the inked serosal surface (*green arrows*). **c** There is diffuse thickening of the gastric wall by infiltrative tumor without obvious disruption of the mucosal surface, grossly consistent with linitis plastica



generally flat lesions with extensive infiltration and very little discernible demarcation; the term linitis plastica is applied when a gastric carcinoma exhibits a type IV pattern of growth and involves the majority of the gastric wall (Fig. 13c) [44].

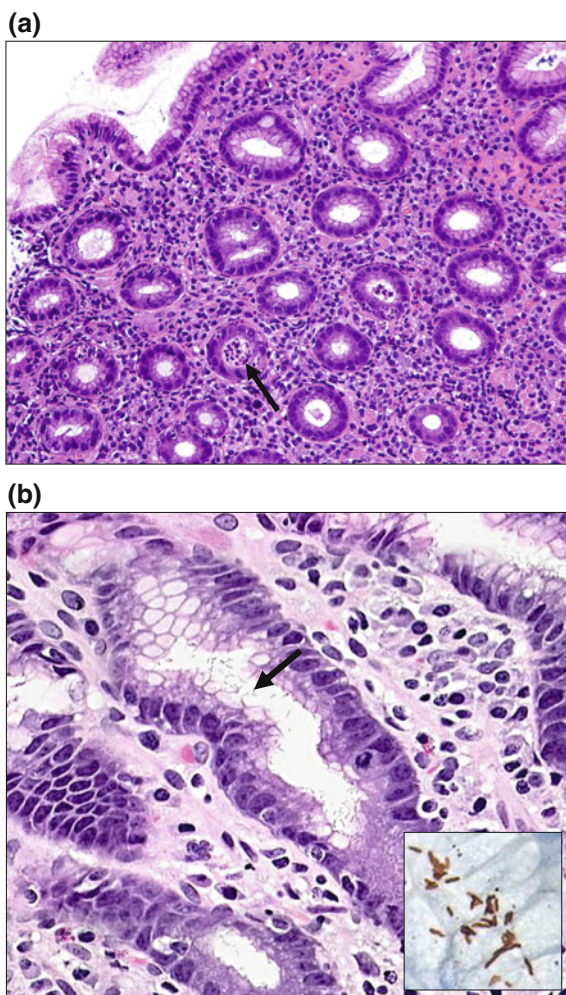
Although seemingly straightforward, there has been some ambiguity in the distinction between cancers arising from the esophagus and gastroesophageal junction (GEJ) and those arising from the gastric cardia. This may be difficult to determine histologically due to overlapping microscopic features of the two entities, and there has even been some disagreement as to whether the gastric cardia is anatomically native mucosa or a metaplastic/reactive process to esophageal reflux or other insults [12]. The 7th AJCC Cancer Staging Manual addresses these difficulties by defining esophageal carcinoma as any tumor arising 5 cm or less from—and also involving—the gastroesophageal junction; tumors not fulfilling these criteria should be staged as authentic gastric carcinomas [60].

3.2.1 Microscopic Pathology

Intestinal-type carcinomas are usually preceded by a well-characterized progression of premalignant lesions (as opposed to diffuse-type carcinomas, which usually lack coincident precursor lesions) [10]. This process may be instigated by infection with *H. pylori*, which incites chronic gastritis characterized by infiltration of the lamina propria by chronic inflammation (plasma cells, lymphocytes) with the addition of neutrophilic infiltration in active cases (Fig. 14a and b). The next step, intestinal metaplasia, occurs when the gastric foveolar and glandular epithelium is replaced by intestinal-type epithelium, which is histologically characterized by columnar cells with small, oval, basally oriented nuclei and voluminous, basophilic (blue) apical cytoplasm. This is in stark contrast to the polymorphic cell population of fundic gland epithelium of the gastric body and the pale mucinous epithelium found in the antrum. Goblet cells (pale columnar cells with a large apical mucin droplet) are interspersed throughout intestinal-type epithelium (Fig. 15a and b); they are readily visualized on low power microscopy and offer a conspicuous indication that gastric epithelium has undergone intestinal metaplasia [11, 21]. Once intestinal metaplasia is established, dysplasia may then occur within the metaplastic epithelium which is subclassified into low-grade or high-grade dysplasia depending on the severity of both cytologic and architectural atypia. Cytologically, dysplasia of gastrointestinal epithelium is characterized by optically dark nuclei (hyperchromasia) which usually exhibit a coarsely granular chromatin pattern. In low-grade lesions, dysplastic nuclei may become enlarged, elongated (“pencillate”), and pseudostratified. At low power, these changes impart an overall darkness or “blueness” to the dysplastic epithelium. High-grade dysplastic nuclei feature exaggerated and variable enlargement/irregularity of the nuclear envelope (nuclear pleomorphism) with a higher ratio of the size of the nucleus to that of the cytoplasm (nucleocytoplasmic/N:C ratio). High-grade dysplasia exhibits even more striking architectural atypia, with “back-to-back” (cribriform) gland formation and a generally disorganized appearance when compared to benign glandular epithelium.

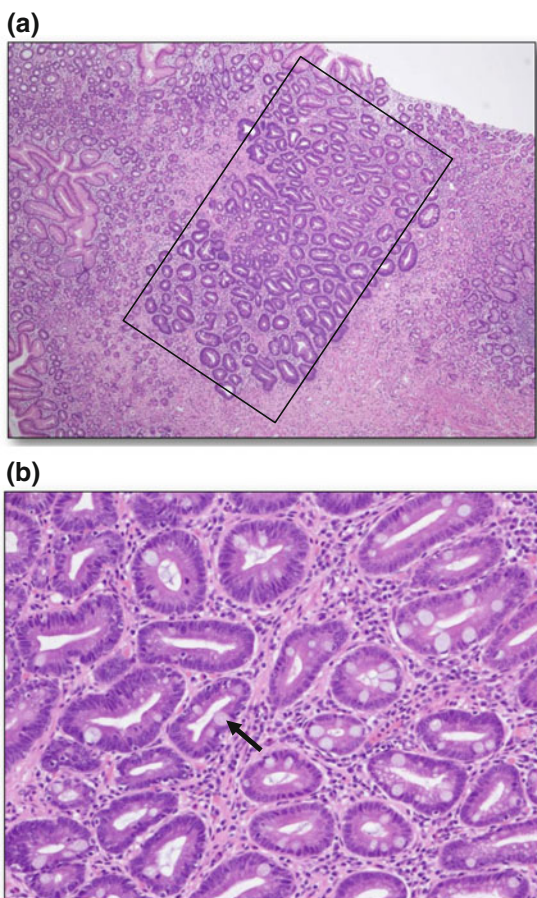
As alluded to previously, gastric adenocarcinomas have historically been categorized into two main histologic groups per the Lauren classification [34]:

Fig. 14 *Helicobacter pylori* gastritis. **a** There is dense infiltration of the lamina propria by chronic inflammation, primarily plasma cells and scattered lymphocytes. There is also an acute gastritis present as demonstrated by neutrophils present within the gastric pits (arrow). **b** At higher power, seagull-shaped spirochetes are noted within the lumen of gastric pits (arrow) and these *Helicobacter pylori* organisms stain positively by immunohistochemistry (inset)



intestinal-type and diffuse-type. Tumors can be of a mixed type or even classified as indeterminate to encompass unusual morphologies which do not fit well into the aforementioned categories. Approximately 54 % of gastric carcinomas are of the intestinal type, 32 % are diffuse type, and 15 % are indeterminate [22]. Intestinal-type carcinomas, as the name suggests, bear striking resemblance to carcinomas arising more distally from intestinal epithelium. Histologically, they are composed of irregular glandular and/or cord-like arrangements of cells which permeate the surrounding stroma in an infiltrative pattern (Fig. 16a). Well-differentiated adenocarcinomas tend to recapitulate glandular architecture in the majority of the tumor, while poorly-differentiated lesions generally display a solid (sheet-like) pattern of growth with high mitotic rates and highly atypical and pleomorphic nuclei (Fig. 16b, c). The stroma surrounding these invasive tumors

Fig. 15 Gastric mucosa with intestinal metaplasia. **a** Focus of intestinal metaplasia (*black box*) seen in a case of nearby adenocarcinoma. At low power, the metaplastic glands have a darker staining quality than the adjacent native glandular epithelium (*far left and right* portion of image). **b** High-power magnification demonstrates bland, basally oriented nuclei and interspersed pale, goblet cells (*arrow*), virtually indistinguishable from normal intestinal epithelium



often displays gray-blue coloration (in contrast to the eosinophilic or pink normal stromal collagen) with numerous spindle-shaped fibroblasts which architecturally contour around the invading tumor. Known as desmoplasia, this phenomenon is a fibroblastic reaction to the infiltrating tumor and can be a helpful histologic clue for the low-power identification of invasive glands (Fig. 16a).

In contrast, diffuse-type gastric carcinomas are composed of discohesive cells which widely infiltrate the gastric stroma either singly or in small clusters. There is no glandular architecture, but lace-like cords of neoplastic cells may occasionally be seen. Signet ring cell-type gastric carcinomas are a subtype of diffuse cancers which contain at least 50 % signet ring cells which are histologically defined by a large, gray-blue intracytoplasmic mucin droplet which peripherally displaces the cell's nucleus and deforms it into a crescent shape (Fig. 17). These tumors are very poorly demarcated and may extensively permeate the gastric wall. Cytokeratin immunohistochemistry can be helpful in detecting inconspicuous signet ring cells

Fig. 16 Intestinal-type carcinoma. **a** This well-differentiated intestinal-type carcinoma demonstrates irregular, infiltrative glands with hyperchromatic nuclei with surrounding *gray-blue*, desmoplastic stroma (*arrows*). **b** This poorly-differentiated intestinal-type adenocarcinoma demonstrates a lobular, sheet-like growth at low power, while at high-power **c** the tumor cells are highly pleomorphic and exhibit an atypical ringed mitosis (*arrow*)

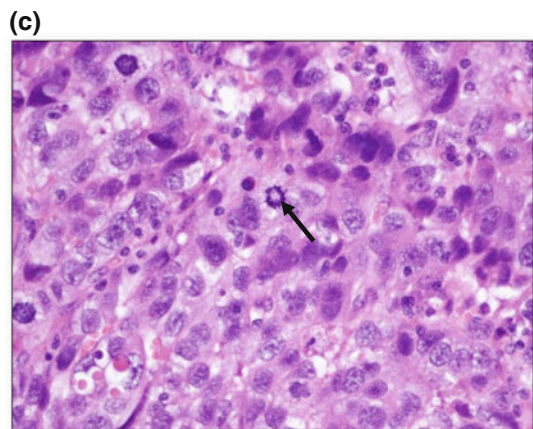
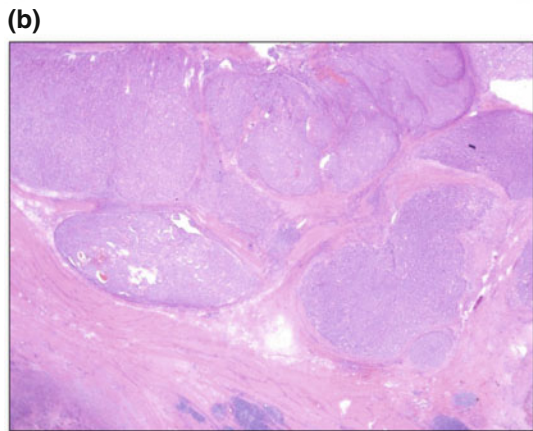
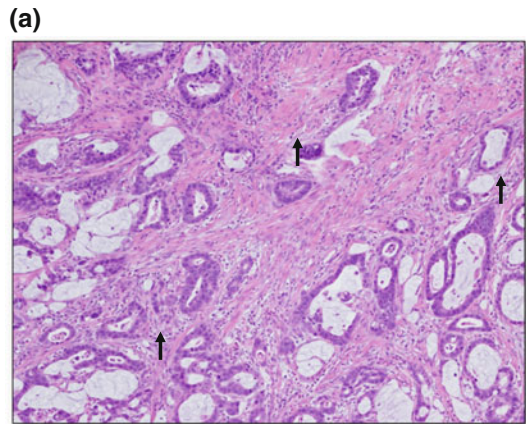
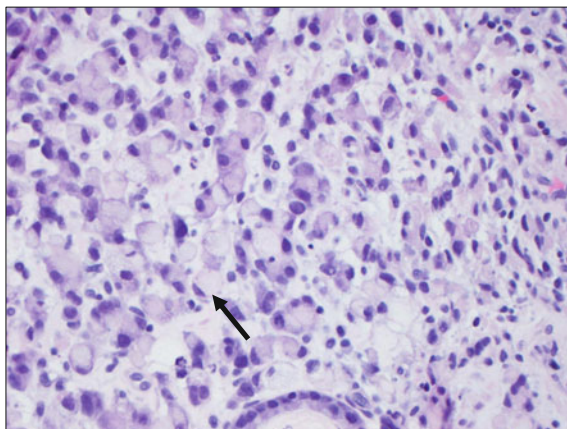


Fig. 17 Diffuse-type carcinoma. These discohesive, malignant cells have a prominent cytoplasmic mucin vacuole (*arrow*) which displace and compress the nucleus to the periphery. The nuclei are pleomorphic and exhibit significant atypia



infiltrating the lamina propria, as early stage lesions may appear quite innocuous at first glance on light microscopy. In cases of macroscopic involvement of most or all of the stomach by cancer, the stomach may assume a thickened and stiff morphology which lends itself to the term “linitis plastica” (leather bottle stomach, Fig. 13c). Linitis plastica most commonly occurs in the setting of diffuse-type carcinoma; however, intestinal-type carcinomas have rarely been shown to produce this macroscopic characteristic as well [20].

In addition to the two broad aforementioned histologic categories, the 2010 WHO Classification of Tumors of the Digestive System introduced an alternative and more specific classification system which addresses tumors with features that might not have otherwise fit well into strictly intestinal versus diffuse types [35]:

Tubular adenocarcinoma: These tumors are characterized by branching glands which range from compressed and slit like to large and dilated. The epithelium ranges from columnar to cuboidal and the cytoplasm may range tinctorially from dark to clear. Desmoplasia may be present, and these tumors range from well- to poorly differentiated architecturally. This type is roughly analogous to the intestinal-type carcinoma of the Lauren classification.

Papillary adenocarcinoma: Papillary carcinomas are generally well-differentiated and predominantly feature exophytic growth and villus-like architecture, with finger-like projections that are lined by neoplastic cuboidal or columnar epithelium and contain a fibrovascular core.

Mucinous adenocarcinoma: The primary feature of these tumors is glandular-type epithelium with exuberant production of mucin, and is analogous to mucinous carcinoma seen in other organs such as the breast and colon. Strips or clusters of neoplastic cuboidal or columnar cells may detach and float within the mucin pools. The mucin itself stains light blue and has a “wispy” character on hematoxylin and eosin (H&E) stained slides. Largely acellular mucin lakes may be seen dissecting throughout the stroma. In order to qualify as a mucinous

carcinoma, at least 50 % of the tumor must consist of extracellular mucin. Occasionally, signet ring-type cells may be seen, but should not be the predominant cell type to qualify for this category.

Poorly cohesive carcinoma, including signet ring cell carcinoma: Analogous to diffuse carcinoma of the Lauren classification system, poorly cohesive carcinomas feature poorly circumscribed tumors with tumor cells which infiltrate singly or in small clusters. Signet ring cell-type carcinomas are a subtype of this group; other tumors include those featuring lymphoid, histiocytoid (resembling macrophages), eosinophilic, or bizarre cell morphology so long as the overall architectural pattern is that of discohesive growth and poor circumscription.

3.3 Molecular Pathology

The majority of sporadic gastric carcinomas (85 %) show an accumulation of various structural and numerical chromosomal changes including translocations, sequence amplifications, gains or losses of chromosomes, etc. Gains of 3q, 7q, 13q, 17q, and 20q as well as losses of 4q, 5q, 6p, 9p, 17p, and 18q are frequently detected by comparative genomic hybridization [21]. Numerous genetic and epigenetic events have been also been described, and carcinogenesis sequence paradigms have been attempted in gastric cancer similarly to those that are widely accepted in colorectal cancer. Generally, gastric carcinogenesis involves the accumulation of mutations of tumor suppressor genes (e.g., *TP53*), activation of telomerase, aberrations of adhesion molecules and cell cycle regulators, and epigenetic factors such as CpG island methylation and silencing of mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) via promoter hypermethylation [65]. As with some breast carcinomas, amplification of human epidermal growth factor 2 (*HER2*) is now a recognized driver of tumorigenesis in 7–34 % of gastric carcinomas. Tumors with amplification of *HER2* are susceptible to targeted therapy with trastuzumab; for this reason, assessment of *HER2* status by immunohistochemistry or FISH is recommended for all gastric cancers at initial diagnosis [50].

In the case of diffuse gastric cancers, a genetic anomaly of note is mutation of the gene encoding the intercellular adhesion protein E-cadherin (*CDH1*). E-cadherin is a calcium-dependent transmembrane protein that connects to the actin cytoskeleton of the cell, helping to maintain normal cellular morphology and cell-to-cell attachment. Loss of *CDH1* is reflected morphologically by the total loss of cell cohesion that is microscopically characteristic of diffuse carcinomas. Germline mutations in *CDH1* have been implicated in familial clusters of diffuse gastric cancers, an entity now known as hereditary diffuse gastric cancer (HDGC). Progression to carcinoma occurs in a “two-hit” fashion, in which a susceptible individual (carrier of the *CDH1* germline mutation) incurs a sporadic mutation or methylation of the second allele. Approximately 1–3 % of diffuse cancers occur in a hereditary fashion, and the estimated lifetime risk of diffuse gastric cancer in susceptible individuals is 67 % in men and 83 % in women [21]. These tumors

generally present at an early age and behave more aggressively than sporadic tumors; due to this grave prognosis, genetic testing is indicated in the following situations: (1) families with two or more cases of diffuse cancer with at least one diagnosed earlier than 50 years of age; (2) families with three or greater cases of diffuse cancer diagnosed at any age; (3) any patient diagnosed with diffuse cancer before age 35; (4) patients with concurrent diagnoses of diffuse gastric cancer and lobular breast carcinoma (due to the role of *CDH1* loss in the pathogenesis of lobular carcinoma); and (5) families with one case of diffuse gastric carcinoma and at least one other case of either lobular breast carcinoma or signet cell carcinoma of the colon [9].

3.4 Prognostic Factors

As with many cancers, one of the most important prognostic factors in gastric adenocarcinoma is tumor stage at resection. Other general predictors of favorable prognosis are negative margin status at resection, benign lymph node status, female gender, high socioeconomic status, Hispanic race, intestinal-type histology, tumors originating in the fundus/body/antrum (vs. gastric cardia), age younger than 70 years, absence of venous or lymphatic invasion, carcinoembryonic antigen (CEA) less than 10 ng/mL, and CA19-9 less than 37 µg/mL [30, 31]. Microsatellite instability, present in approximately 15 % of gastric cancers, has also been shown to confer a favorable prognosis [5].

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