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Review

Precancerous lesions of the stomach, gastric cancer and hereditary gastric cancer syndromes

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Summary
Gastric cancer accounts for about 6% of cancers worldwide, being the fifth most frequently diagnosed malignancy and the third leading cause of cancer related death. Gastric carcinogenesis is a multistep and multifactorial process and is the result of the complex interplay between genetic susceptibility and environmental factors. The identification of predisposing conditions and of precancerous lesions is the basis for screening programs and early stage treatment. Furthermore, although most gastric cancers are sporadic, familial clustering is observed in up to 10% of patients. Among them, hereditary cases, related to known cancer susceptibility syndromes and/or genetic causes are thought to account for 1-3% of all gastric cancers. The pathology report of gastric resections specimens therefore requires a standardized approach as well as in depth knowledge of prognostic and treatment associated factors.

Key words: gastric cancer, gastric dysplasia, gastric adenocarcinoma, hereditary gastric cancer syndromes, hereditary diffuse gastric cancer (HDGC)

Introduction

Gastric cancer accounts for about 6% of cancers worldwide, being the fifth most frequently diagnosed malignancy and the third leading cause of cancer related death, behind lung and colorectal cancer. According to the most recent GLOBOCAN cancer estimates, gastric cancer was responsible for over 1,000,000 new cancer cases and 783,000 deaths in 2018 [1]. Although there has been a steady decline in the incidence and mortality of gastric cancer over the last 15 years, as the result of the decrease of *Helicobacter pylori* prevalence and better dietary habits, the absolute incidence rate continues to rise, due to the advancing age of the world population.

Gastric cancer incidence and mortality vary substantially across countries and within each country. Incidence rates are elevated (up to 32 cases per 100,000) in Eastern and Western Asia. Zones of low incidence (< 7 cases

per 100,000) are Northern America, Northern Europe, and most regions of Africa [1]. In Italy, gastric cancer ranks eighth among all cancers, with 12,803 new cases and 9,457 deaths in 2018 [1]. The poor clinical outcome of gastric cancer is mainly due to late diagnosis, poor response to therapeutic regimens and the highly heterogenous nature of the disease [2].

Gastric carcinogenesis is a multistep and multifactorial process and is the result of the complex interplay between genetic susceptibility and environmental factors. Risk factors predisposing to gastric cancer include *Helicobacter pylori* infection, tobacco smoking, dietary habits [3] (high intake of salt-preserved, smoked foods, red and processed meat, low intake of fresh fruit and vegetables), and Epstein-Barr virus (EBV) infection [4], as well as microbial community modifications by long-term use of proton-pomp inhibitors [5]. A number of precancerous conditions have been recognized, such as chronic atrophic gastritis and intestinal metaplasia due to *Helicobacter pylori* infection or autoimmunity (pernicious anemia), peptic ulcer disease, gastric stump after partial gastrectomy and gastric polyps.

Although most gastric cancers are sporadic, familial clustering is observed in up to 10% of patients. Among them, hereditary cases, related to known cancer susceptibility syndromes and/or genetic causes are thought to account for 1-3% of all gastric cancers [6,7]. The three major hereditable syndromes that primarily affect the stomach are hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma, proximal polyposis of the stomach (GAPPS), and familial intestinal gastric cancer (FIGC).

Precancerous lesions

Atrophic gastritis and intestinal metaplasia

Gastric carcinogenesis is a multistep process which involves, in most cases, a progression from normal mucosa through chronic gastritis (chronic inflammation of the gastric mucosa), mucosal atrophy (loss of gastric glands) and intestinal metaplasia (substitution of gastric epithelium by intestinal epithelium) to dysplasia (intraepithelial neoplasia) and carcinoma. This sequence of events may last several years and has been designated as the Correa's cascade of multistep gastric carcinogenesis [8]. According to this model, long standing inflammation is the primary pathogenic factor leading to gastric cancer development.

Among environmental factors leading to inflammation-mediated gastric cancer, *Helicobacter pylori* infection is associated with almost 90% of new cases of non-cardia gastric cancers [9] and was classified as a type I carcinogen by the WHO in 1994. Approximately half of the world's population is infected with *Helicobacter pylori*, however, only a small fraction will end up developing gastric carcinoma, suggesting that additional factors participate in the carcinogenic process, including *Helicobacter pylori* virulence factors, genetic susceptibility, diet, smoking, and possibly other bacteria species [10]. *Helicobacter pylori* virulence factors that appear to influence the pathogenicity of the bacterium, as well as the risk of gastric cancer development, include CagA (cag pathogenicity island-encoded cytotoxin associated gene A) and VacA (vacuolating cytotoxin A) [11], while polymorphisms of genes involved in initiation and modulation of the inflammatory response, such as genes codifying IL-1β, IL-1 receptor antagonist, IL-10 and TNFα, are host genetic susceptibility factors associated with individual or familial susceptibility to carcinogenesis mediated by *Helicobacter pylori* infection [12]. Although the magnitude of risk is not uniformly defined, atrophic gastritis caused by autoimmunity (pernicious anemia) is associated with an increased risk of dysplasia and adenocarcinoma [13], as well as neuroendocrine neoplasms and gastric epithelial polyps, such as intestinal-type adenomas and pyloric gland adenomas.

Several classification systems for chronic gastritis have been developed, including the Sydney classification system [14], the Gastric Risk Index [15] and the Operative Link on Gastritis Assessment (OLGA) system [16]. These staging systems, particularly the five-tiered (0-IV) OLGA system, provide a basis for predicting gastric cancer risk associated with atrophic gastritis and intestinal metaplasia and guide clinical surveillance [17].

Well established evidence links intestinal metaplasia to intestinal-type gastric cancer [18]. Complete intestinal metaplasia shows goblet cells, absorptive enterocytes with luminal brush border and intestinal mucin (MUC2) expression. In contrast, incomplete intestinal metaplasia displays globet cells, absorptive cells without brush border and co-expression of intestinal and gastric (MUC5AC, MUC6) mucins [19]. Reliable indicators of gastric cancer risk include the topographical extent of intestinal metaplasia and the degree of incomplete-type intestinal metaplasia [20].

Another pattern of metaplasia, which is believed to represent an alternative pathway to gastric neoplasia, is pseudopyloric or spasmolytic polypeptide-expressing metaplasia (SPEM), which expresses trefoil factor family 2 (TFF2) spasmolytic polypeptide and represents the metaplastic replacement of oxyntic glands by mucin secreting antral-like glands. SPEM develops in the gastric body and fundus and has been associated with chronic *Helicobacter pylori* infection and development of gastric cancer [21].

Gastric dysplasia

Gastric dysplasia is defined as unequivocal neoplastic changes in the gastric epithelium, without evidence of lamina propria invasion. The diagnostic criteria are based on the presence of cellular atypia, abnormal differentiation, architectural disorganisation and increased mitotic activity. Endoscopically, gastric dysplasia may present as flat, depressed or polypoid lesions (the latter may be referred to as gastric – intestinal type and foveolar type – adenomas). It may arise de novo or may occur within pre-existing benign sporadic polyps, namely hyperplastic polyps and fundic gland polyps or hamartomatous polyps, such as juvenile polyps and Peutz-Jeghers polyps.

On the basis of the histomorphological profile, gastric dysplasia may be classified as intestinal or foveolar (gastric) type. *Intestinal type dysplasia* shows features resembling colonic adenomas, with tubular glands lined by columnar cells with overlapping, pseudostratified and penicillate nuclei, which can be hyperchromatic and/or pleomorphic. Differentiation towards goblet cells, absorptive cells and Paneth cells may be observed. Intestinal type dysplasia shows immunoreactivity for MUC2, CD10 and CDX2 [22]. The *foveolar (gastric) phenotype* is characterized by cuboidal to low columnar cells resembling gastric foveolar cells, with round to oval nuclei and clear or eosinophilic cytoplasm. Gastric differentiation may be confirmed by MUC5AC and MUC6 expression. Using immunohistochemistry, hybrid or mixed cases may also occur, with both intestinal and gastric marker expression, as well as null cases, negative for the aforementioned markers. Foveolar type dysplasia is more likely to be high-grade and is associated more frequently to gastric adenocarcinoma [22].

Dysplasia is graded as low grade or high grade on the basis of architectural distortion, nuclear and cytoplasmic cell features and mitotic activity. In low grade dysplasia, glandular architecture is relatively preserved, cellular pleomorphism is mild or absent, nuclei maintain basal polarity and mitotic activity is not markedly increased. High grade dysplastic features include complex glandular architecture, marked cytologic atypia with large nuclei and prominent nucleoli, loss of cell polarity and frequent mitotic figures [23]. Distinction between high-grade dysplasia and intramucosal intestinal adenocarcinoma may be challenging, especially in small biopsy samples, and there is only limited consensus about diagnostic criteria, especially between Asian and Western pathologists. Helpful features for the diagnosis of intramucosal adenocarcinoma include marked glandular crowding, cribriform and crawling pattern, budding, infiltration of isolated cells and intraglandular necrotic debris (Fig. 1). The presence of desmoplasia is not necessary for the definition of stromal invasion. The distinction between reactive/regenerative changes and true dysplasia may be difficult, especially in small biopsies and specimens with technical artefacts. For these cases, the term “indefinite for dysplasia” may be applied. Gastric dysplasia limited to the pit region, without superficial epithelial involvement, is defined as crypt dysplasia [24].

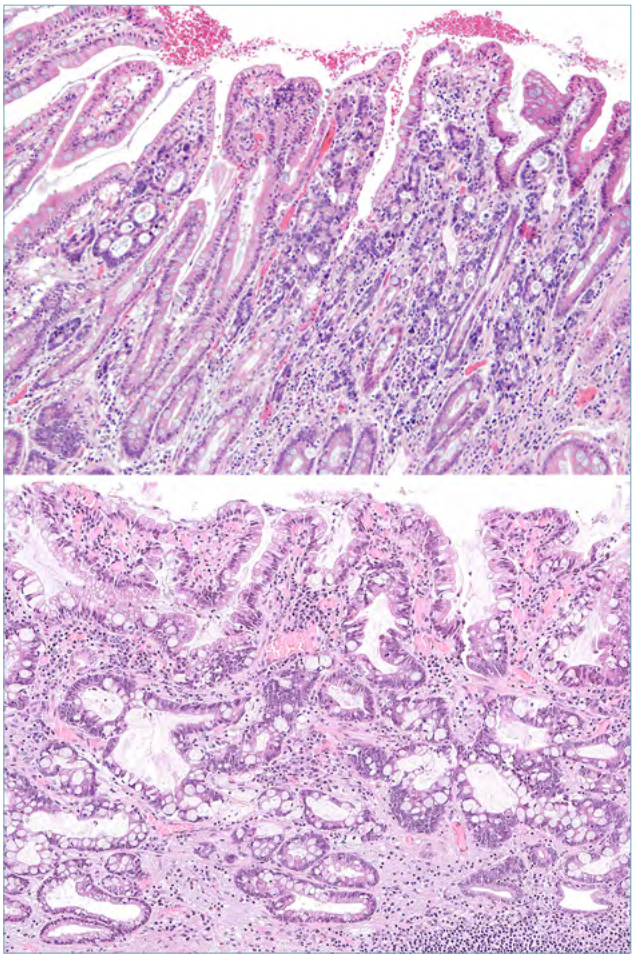

Figure 1. Two examples of intramucosal gastric carcinoma. In contrast to high grade dysplasia, intramucosal carcinoma shows marked glandular crowding and cribriform pattern (upper image, HE, magnification 10x). The bottom image shows a very well differentiated intramucosal carcinoma with crawling pattern (HE, magnification 10x).

Gastric adenomas

A recent classification proposed by Hackeng WM et al. [25]. distinguishes gastric polyps according to the gastric mucosa compartment from which the gastric polyp arises. Gastric adenomas arising from the foveolar compartment include foveolar type adenomas (arising

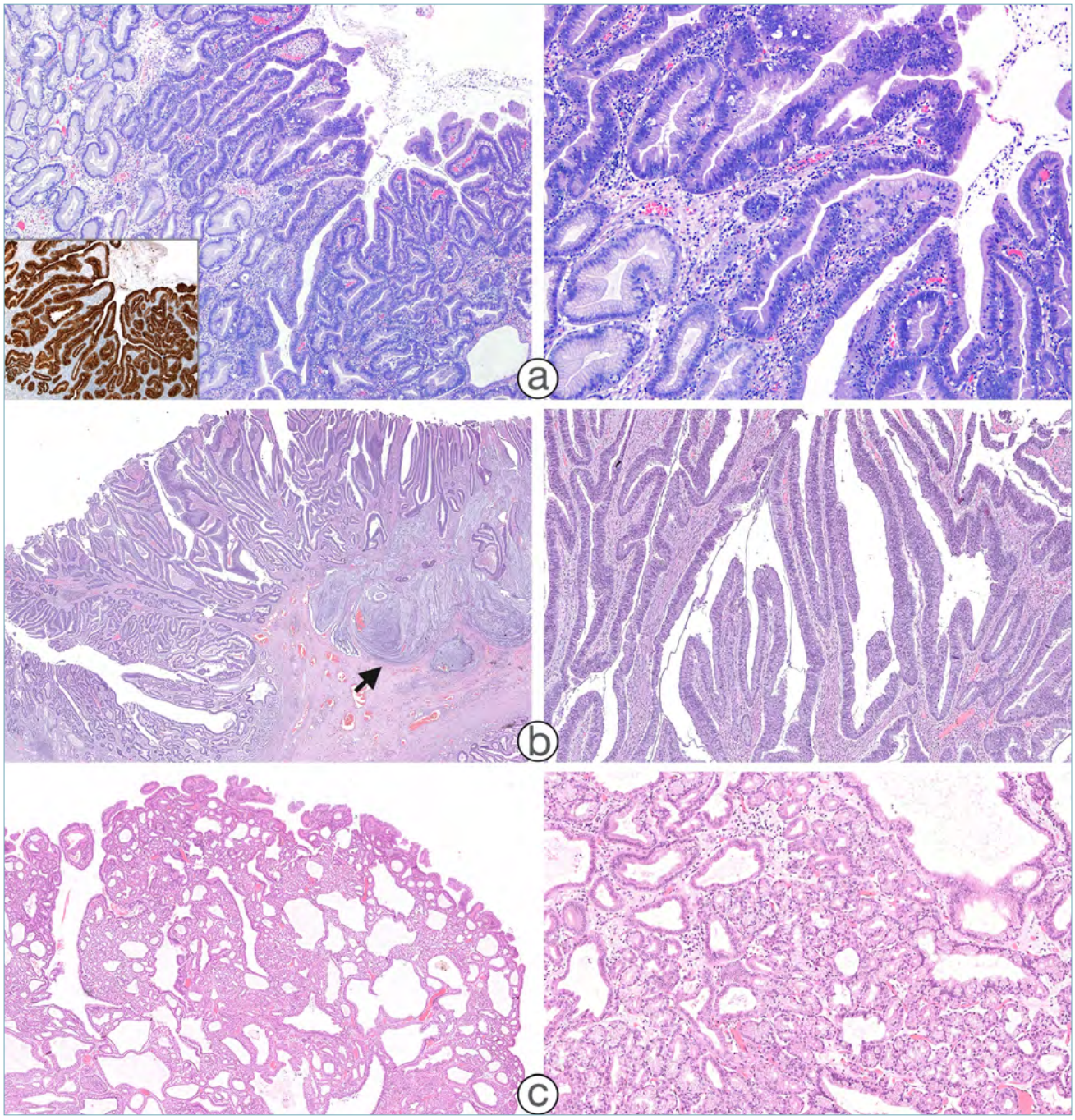

Figure 2. Gastric adenomas: (a) foveolar type adenoma with low grade dysplasia (HE, left image, magnification 40x, right image, magnification 10x) showing diffuse immunoreactivity for MUC5AC (inset); (b) intestinal type adenoma associated to mucinous carcinoma invading the submucosa (arrow) (HE, left image, magnification 4x); the image on the right represents an area of intestinal-type low grade dysplasia with tubular/villous morphology (HE, magnification 10x); (c) pyloric gland adenoma (HE, left image, magnification 4x, right image, magnification 20x).

from foveolar epithelium without intestinal metaplasia) (Fig. 2a) and intestinal type adenomas (arising from foveolar epithelium with intestinal metaplasia) (Fig. 2b). Gastric adenomas arising from the glandular compartment include pyloric gland adenoma (PGA) (Fig. 2c) and oxyntic gland adenoma (OGA). Consistent with

their glandular histogenesis, OGAs and PGAs show diffuse immunoreactivity for MUC6.

PGAs consist of closely packed tubules or dilated glands of pyloric type epithelium, lined by cuboidal/low columnar cells with pale, clear or slightly eosinophilic cytoplasm. PGAs may occur in syndromic contexts, namely familial adenomatous polyposis (FAP) and Lynch syndrome [26].

OGAs is composed of dysplastic glands showing variable differentiation to chief and parietal cells. There is a morphological continuum between OGA and gastric adenocarcinoma of fundic gland type. Whether they are distinct lesions, the former representing the precursor lesion of the latter, or represent a morphological spectrum of the same lesion is still debated [27].

Benign gastric polyps with possible gastric dysplasia and gastric cancer

Hyperplastic polyps (HPs) are benign gastric epithelial lesions consisting of hyperplastic and cystically dilated foveolar epithelium, in a background of prominent inflammatory changes. As HPs represent a hyperproliferative response to tissue injury, most of them arise in a background of longstanding gastric mucosal inflammation and are the prevalent polyp type in countries with a high prevalence of *Helicobacter pylori* infection. Foveolar or intestinal type dysplasia and adenocarcinoma (intestinal type or diffuse type) may arise in about 2% of larger HPs [28] (Fig. 3). Copy number alterations and TP53 mutations are restricted to the adenocarcinoma component [29].

Fundic gland polyps (FGPs) are benign gastric epithelial lesions composed of disordered, expanded and cystically dilated oxyntic glands lined by parietal and chief cells, as well as mucous neck epithelium. FGPs are the predominant polyp type in Western countries, are associated with the use of proton pomp inhibitors and are inversely related to *Helicobacter pylori* gastritis [30]. FGPs may develop foveolar-type dysplasia, which is usually low-grade (Fig. 4). In sporadic FGPs, dysplasia is rarely observed and the finding of dysplasia should raise suspicion of an inherited syndrome, especially in the case of young patients, multiple FGPs and (in the case of FAP) polyps elsewhere in the gastrointestinal tract. In the syndromic context, dysplasia in FGPs may be observed in gastric adenocarcinoma and proximal polyposis of the stomach (see below) and FAP. The genomic landscape of syndromic and sporadic FGPs is distinctive. FAP-associated FGPs may present second-hit inactivation of the APC gene but no CTNNB1 (beta-catenin) mutations, while sporadic FGPs harbour CTNNB1 mutations and usually lack APC alterations [31].

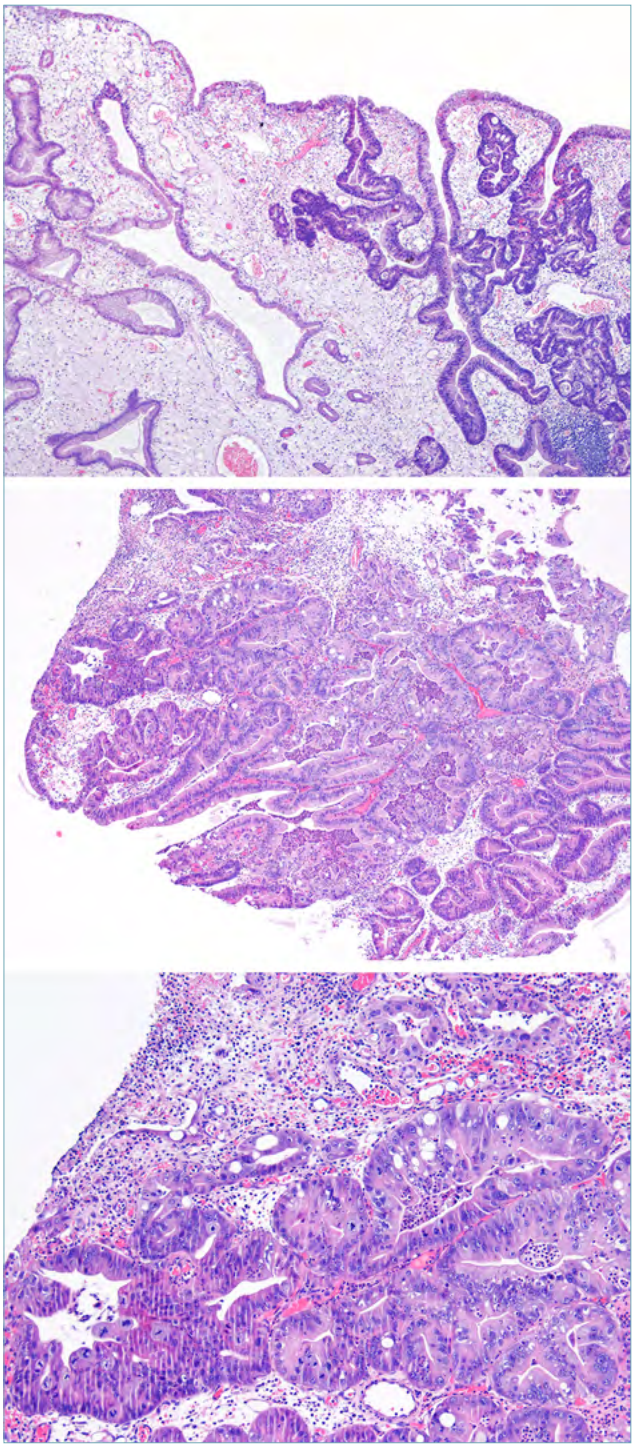

Figure 3. Hyperplastic polyp with dysplasia (HE, upper image 4x) and intramucosal carcinoma (HE, middle image, magnification 40x, bottom image, magnification 10x).

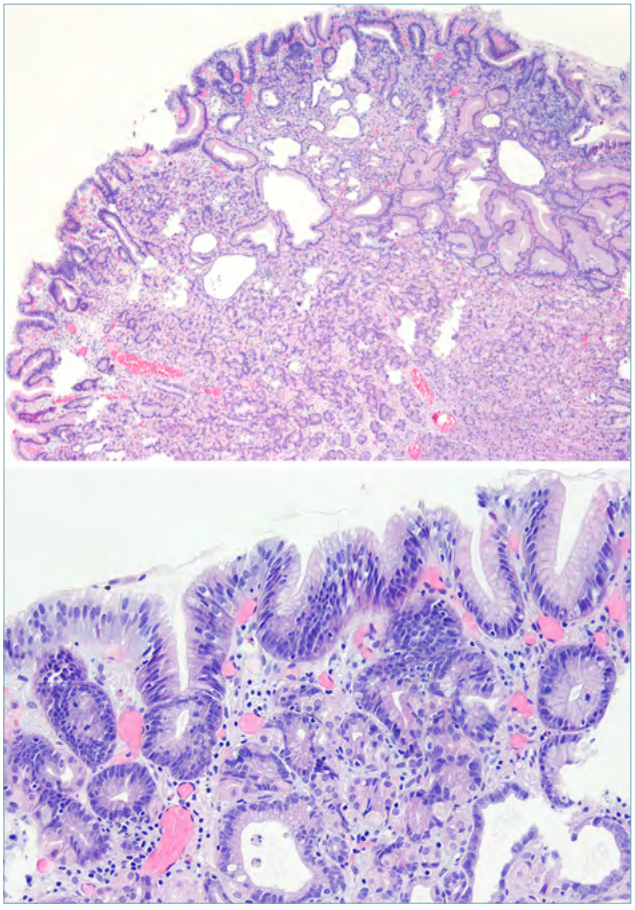

Figure 4. Fundic gland polyp with focus of low grade, foveolar-type dysplasia (upper image, HE, magnification 4x; (upper image, HE, magnification 20x). The patient had attenuated variant of familial adenomatous polyposis.

Gastric cancer

Definitions

Gastric adenocarcinoma is a malignant epithelial neoplasm with glandular differentiation arising from the gastric mucosa and represents a biologically heterogeneous group of tumors with respect to etiology, histogenesis, morphology, and molecular features. Overall, gastric adenocarcinoma accounts for 90-95% of gastric malignancies.

According to the depth of invasion in the gastric wall, gastric cancer is classified as early or advanced. Early gastric cancer is defined as a carcinoma limited to the mucosa (pT1a) or the mucosa and submucosa (pT1b), regardless of tumor size or the presence of lymph-node metastases. Gastric adenocarcinomas invading the muscularis propria and beyond (> pT2) are defined as advanced.

Clinical features

The clinical presentation of gastric cancer is mainly related to topography and stage of the disease. The majority of early gastric cancers are asymptomatic at diagnosis. Screening programs in high-risk populations (Japan, Korea) have resulted in early diagnosis in asymptomatic patients and better overall survival [32]. At advanced disease stage, common signs and symptoms include dyspepsia, epigastric pain, abdominal mass and alarm symptoms ("red flags"), such as dysphagia, significant weight loss, signs and symptoms of gastrointestinal hemorrhage and vomiting.

Endoscopic examination with biopsies is the gold standard method for gastric cancer diagnosis. Image enhanced endoscopy and magnifying endoscopy may improve the detection rate of early gastric lesions [33].

Accurate (TNM) staging is the cornerstone for accurately defining gastric cancer prognosis and therapeutic approaches. Compared to advanced gastric cancers, early gastric cancers have a much better prognosis, with a 5-year survival rate of > 90% after surgical resection. If untreated, 63% of early gastric carcinomas progress to advanced tumors within 5 years [34]. In contrast, advanced and unresectable gastric cancers have a poor prognosis with an expected survival of few months. Endoscopic ultrasonography is the preferred technique for defining the depth of invasion into the gastric wall (pT stage).

Endoscopic resection is recommended for early gastric cancers with low probability of metastasising to lymph nodes. Risk factors associated with the development of nodal metastases, for which surgery with lymph-node dissection should be considered, include submucosal invasion, tumor diameter greater than 20-30 mm, vascular venous or lymphatic invasion, depressed or ulcerated macroscopic subtypes and undifferentiated histology [35]. Treatment for advanced gastric cancer is based on surgery and chemo-radiation therapy. For patients with unresectable gastric cancer, systemic therapy is the only approach, encompassing conventional chemotherapy and targeted therapies. The latter include monoclonal antibodies directed against HER2, VEGFR2 and immune checkpoint inhibitors [36,37]. According to the most recent European recommendations [38] the only established predictive biomarker for the treatment of gastric cancer is HER2 status, evaluated by HER2 immunohistochemistry and ERBB2 in situ hybridization to select patients with unresectable or metastatic gastric cancer for anti-HER2 based therapies. Heterogeneity in HER2 assessment in gastric cancer has been widely documented [39] and this is of practical importance when HER2 evaluation is performed on endoscopic biopsies: a minimum set of 5 biopsies has shown to be necessary for a reliable HER2 assessment [40-41].

Emerging predictive biomarkers for selecting gastric cancer patients who may benefit from immune-checkpoint inhibitor-based immunotherapies include microsatellite instability (MSI)-high status [42], EBV infection [43], PD-L1 expression (combined positive score ≥ 1%) [44], tumor mutation load and density of intra-tumoral CD8+ T-cells [45].
Adverse prognostic factors in resectable cases include higher pT and pN stages [46], limited lymph node dissection, lymphatic and vascular invasion, and involvement of surgical margins.

Microscopic findings and histopathological classifications

Gastric cancer presents a variability of morphological phenotypes, as reflected by the large number of histopathological classifications proposed over time [47]. The histopathological classifications most commonly used include those proposed by Laurén [48] and the World Health Organization (WHO) [23].
The Laurén classification [48] (Tab. I) distinguishes two major types, intestinal and diffuse. The former, is composed of glands or papillae, while the latter shows an infiltrative growth pattern and is composed of tumor cells without cellular cohesion. Tumors presenting both intestinal and diffuse components are termed mixed carcinomas. Solid, poorly differentiated or undifferentiated carcinomas that do not fit in one of these subtypes are placed in the indeterminate category. Despite dating back to 1965, Laurén classification is still relevant, as it distinguishes subtypes with distinct

Table I. Checklist for gastric cancer reporting (based on WHO Classification of Digestive System Tumors, 5th Edition and AJCC Cancer Staging Manual, 8th Edition).

Procedure	Endoscopic resection Partial gastrectomy: specify if proximal, distal, other Total gastrectomy Other
Specimen description	*Endoscopic resection* Dimension of mucosal surface (cm) and depth (cm)
	Gastrectomy Length (cm) of lesser and greater curvature Length (cm) of duodenal and oesophageal segments, if applicable
Macroscopic examination	Tumor not identified macroscopically
	Tumor location (gastric region): cardia, fundus, body, transitional zone, antrum, pylorus
	Tumor location (gastric curvatures and walls): lesser curvature, greater curvature, anterior wall, posterior wall
	Tumor size: greatest dimension (cm) or three dimensions (cm)
	Tumor macroscopic appearance - Borrmann type I: polypoid/fungating - Borrmann type II: ulcerated mass - Borrmann type III: infiltrative neoplasm with ulceration - Borrmann type IV: infiltrative neoplasm without ulceration
Margins	*Endoscopic resection* Mucosal margin - Involved by invasive carcinoma - Involved by dysplasia (low-grade/high-grade) - Uninvolved by invasive carcinoma or dysplasia Deep margin - Involved by invasive carcinoma - Involved by dysplasia (low-grade/high-grade) - Uninvolved by invasive carcinoma or dysplasia
	Gastrectomy Esophageal (proximal) margin - Involved by invasive carcinoma - Involved by dysplasia (low-grade/high-grade) - Uninvolved by invasive carcinoma or dysplasia Duodenal (distal) margin - Involved by invasive carcinoma - Involved by dysplasia (low-grade/high-grade) - Uninvolved by invasive carcinoma or dysplasia Omental (radial) margin - Involved by invasive carcinoma (greater and/or lesser omental margin) - Uninvolved by invasive carcinoma

▶

Table I. continues

Gastric cancer histological subtype	*Laurén classification*[55]: - Diffuse type - Intestinal type - Mixed type - Indeterminate *WHO classification* (major types and rare variants): - Tubular adenocarcinoma - Papillary adenocarcinoma - Tubulo-papillary adenocarcinoma - Poorly cohesive carcinoma: signet ring cell type/not otherwise specified - Mucinous adenocarcinoma - Mixed adenocarcinoma - Gastric squamous carcinoma - Gastric adenosquamous carcinoma - Gastric undifferentiated carcinoma - Gastric cancer with lymphoid stroma - Hepatoid carcinoma - Alpha-fetoprotein producing gastric cancer (adenocarcinoma with enteroblastic differentiation, yolk-sac tumor like carcinoma) - Micropapillary adenocarcinoma - Gastric adenocarcinoma of the fundic gland type - Mucoepidermoid carcinoma - Paneth cell carcinoma - Parietal cell carcinoma
Histologic grade	Only applicable to tubular and papillary adenocarcinoma: - Low grade - High grade
Pathological stage: descriptors	- **m** (multiple primary tumors) - **r** (recurrent) - **y** (post-treatment)
Pathological stage: primary tumor (pT)	- **pTX**: primary tumor cannot be assessed - **pT0**: no evidence of primary tumor - **pTis**: *in situ* SRC carcinoma, pagetoid progression of SRCs, high-grade dysplasia - **pT1a**: tumor invades the lamina propria or muscularis mucosae - **pT1b**: tumor invades the submucosa - **pT2**: tumor invades the muscularis propria - **pT3**: tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures - **pT4a**: tumor invades the serosa (visceral peritoneum) - **pT4b**: tumor invades adjacent structures/organs
Lymph node examination	Number of lymph nodes involved - Lesser omentum - Greater omentum - Other Number of lymph nodes examined - Lesser omentum - Greater omentum - Other *Ratio* between lymph nodes involved and examined
Pathological stage: regional lymph nodes (pN)	- **pNX:** regional lymph node(s) cannot be assessed - **pN0:** no regional lymph node metastasis - **pN1:** metastasis in one or two regional lymph nodes - **pN2:** metastasis in three to six regional lymph nodes - **pN3a:** metastasis in seven to 15 regional lymph nodes - **pN3b:** metastasis in 16 or more regional lymph nodes
Pathological stage: distant metastasis	- Not applicable (pM *status* required only if confirmed pathologically) - **pM1**: distant metastasis(es) (specify site)
Lymphovascular invasion	- Not identified - Present - Cannot be determined

▶

Table I. continues

Perineural invasion	- Not identified - Present - Cannot be determined
Treatment effect	- No known presurgical therapy - Present • Complete response (no viable cancer cells) – score 0 • Near complete response (single or rare small groups of cancer cells) – score 1 • Partial response (evident tumor regression but more than single or rare small groups of cancer cells) – score 2 • Poor or no response (no evident tumor regression) – score 3 - Cannot be determined
Additional findings	- *Helicobacter pylori* infection - Chronic gastritis (lymphoid follicles, neutrophilic activity, erosion/ulceration) - Glandular atrophy - Intestinal metaplasia - Dysplasia - Polyps: specify type
Ancillary studies	Add any relevant ancillary study performed
Comments	Add any relevant comment

epidemiologic settings, clinicopathologic profiles and biological behaviors. As an example, in view of their cohesive nature, intestinal type gastric cancers have the ability to survive more easily into venous vessels and tend to metastasise haematogenously, while the poorly cohesive phenotype of diffuse gastric cancer tends to disseminate through peritoneal surfaces. Mixed gastric cancer shows a poorer prognosis compared to intestinal or diffuse types [49] and a dual metastatic pattern (hematogenous metastases and peritoneal dissemination with lymph node metastases) [50], probably because of the cumulative adverse effect of the two components within a single tumor.

The WHO classification [23] (Tab. I) distinguishes five main histopathological subtypes of gastric cancers (Fig. 5): tubular adenocarcinoma, composed of tubular, glandular or acinar structures of variable diameter and various degrees of differentiation (some solid carcinomas may be classified as high-grade tubular adenocarcinomas); papillary carcinoma, showing finger-like papillary architecture, eventually admixed with glandular structures (tubulo-papillary phenotype); poorly cohesive carcinoma, composed of tumor cells isolated or in small clusters lacking cellular cohesion; mucinous adenocarcinoma, defined by the presence of mucin pools accounting for > 50% of the tumor; and mixed carcinomas, presenting a distinct tubulo-papillary and poorly cohesive component. In mixed carcinomas, the two components may be intermingled, adjacent, or completely separated. Providing that the two components are clearly identified within the tumor, there is no minimum cell percentage defining this entity.

Grading system (low-grade or high-grade gastric adenocarcinoma) applies primarily to tubular, papillary and tubulo-papillary subtypes [23]. Tubular and papillary carcinomas roughly correspond to intestinal type gastric cancers, while poorly cohesive carcinomas correspond to the diffuse subtype by Laurén.

The 2019 WHO Classification of digestive system tumors stresses the importance of distinguishing different subtypes within the poorly cohesive carcinoma category, based on presence and quantity of signet ring cells. By definition, a signet ring cell has an abundant mucin vacuole filling the cytoplasm and pushing the nucleus at the cell periphery. Poorly cohesive carcinomas of the signet ring cell type are composed predominantly or exclusively (*e.g.* > 90%) of signet ring cells, while non-signet ring cell type (*i.e.* not otherwise specified) poorly cohesive carcinomas are composed (or show a component) of poorly cohesive and infiltrating cells without a classic signet ring cell morphology. It is important to recognise this latter subtype of poorly cohesive gastric cancer, as it presents poorer prognosis when compared to pure signet ring cell carcinomas [51].

The gastric cancer histopathological classification proposed by the Japanese Gastric Cancer Association (JGCA) is mainly used by Asian pathologists [52]. Noteworthy, in the last version of the JGCA and the WHO classifications, gastric cancer expert pathologists have built a table showing the similarities of the two classification systems and corresponding entities.

To improve standards of gastric cancer reporting, macroscopic and histological examination should follow a specific checklist, as presented in Table I.

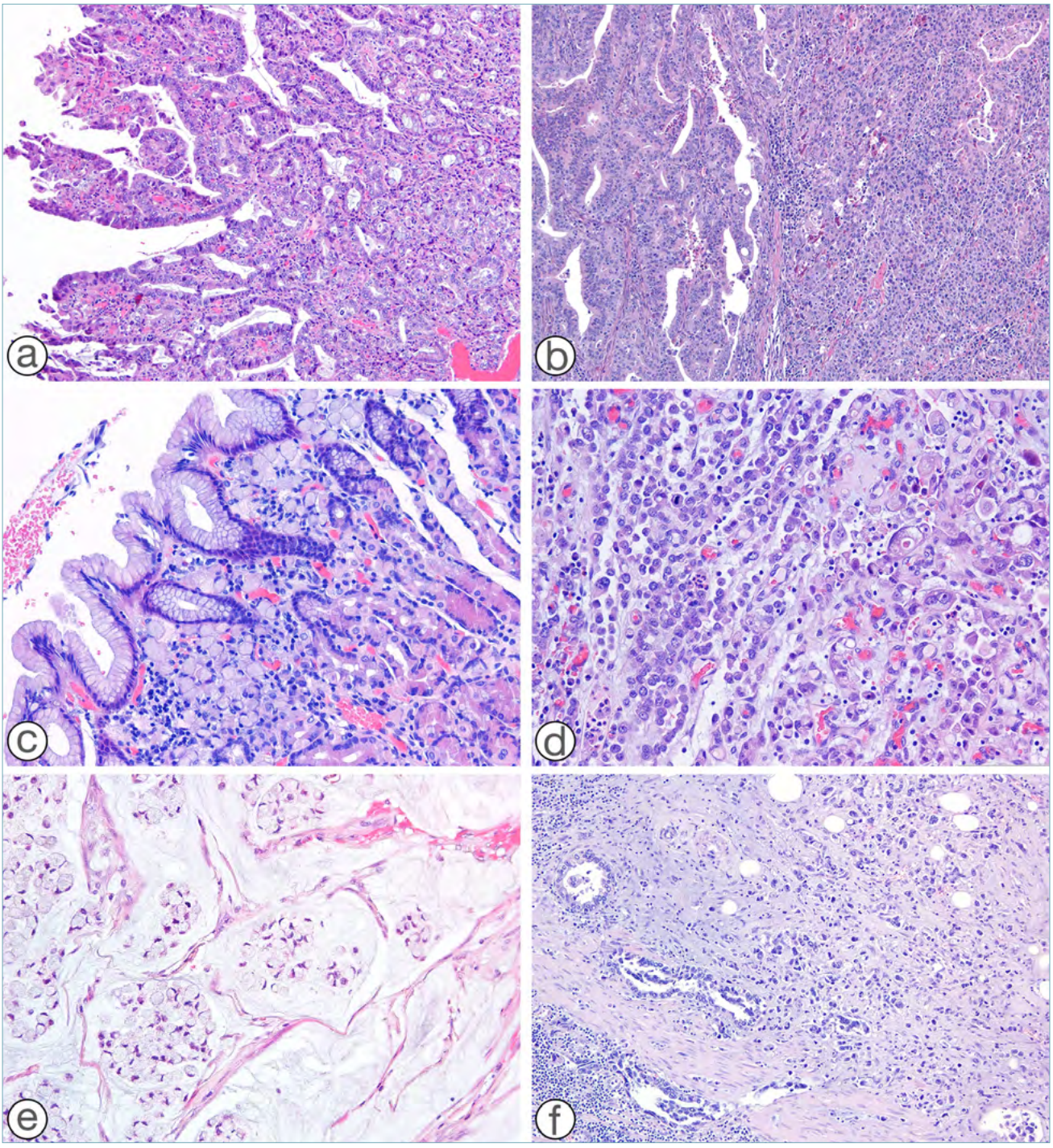

Figure 5. Main histopathological subtypes of gastric cancer: (a) papillary and tubulo-papillary gastric adenocarcinoma (HE, magnification 10x); (b) tubular adenocarcinoma with solid (high grade) areas (HE, magnification 10x); (c) poorly cohesive gastric cancer of the signet ring cell type (HE, magnification 20x); this tiny intramucosal *focus* was found in a prophylactic gastrectomy specimen in a *CDH1* variant carrier; (d) poorly cohesive gastric cancer not otherwise specified (HE, magnification 20x); in this case the poorly cohesive cells show pleomorphic and plasmacytoid features; (e) mucinous adenocarcinoma, with and signet ring cells floating in mucin lakes (HE, magnification 20x); (f) mixed gastric cancer (HE, magnification 20x).

Early gastric cancer

Early gastric cancer (EGC) is carcinoma limited to the gastric mucosa and/or submucosa regardless of lymph node status with good prognosis [52]. Unfortunately, some EGC will have nodal metastases and recent studies have focused on key parameters that could be associated with worse prognosis [53]. In particular, size, depth of infiltration, and histological type of tumors, as well as the distribution of nodal metastases, are predictors of worse survival in this subset of tumors [54].

A dated but useful classification (see Tab. II) was introduced by Kodama [55] in 1983 that identifies growth patterns of EGC and correlates them with prognosis; more recent studies [56] have confirmed the importance of this classification which should be part of the pathology report both in surgical specimens but more importantly in endoscopic resections (Penetrating A growth subtype has a 10 year prognosis of 74% compared to 94% of non-penetrating A type).

Immunohistochemical biomarkers and molecular subtypes

Gastric cancer is the result of accumulated genomic damage that affects essential cellular functions for cancer development. Multiple gene mutations, somatic copy number alterations, epigenetic and transcriptional changes have been detected in gastric cancer, highlighting its molecular heterogeneity. Through high-throughput genomic analysis, several groups have analyzed and deciphered the molecular alterations of gastric cancer at high resolution, attempting to achieve integrated molecular classification schemes which recognise molecular entities with different molecular signatures and clinical phenotypes. These classifications include the Singapore-Duke group classification [57], based on gene expression profiling, and the molecular classifications proposed by The Cancer Genome Atlas (TCGA) [58], and the Asian Cancer Research Group (ACRG) [59], both based on the integrative analysis of multiple genomic and proteomic data. These molecular classifications have been proposed as a roadmap for gastric cancer prognostic evaluation and targeted therapy approaches. However, the three molecular classifications overlap only partially, highlighting the need for a consensual patient stratification.

The landmark study of gastric cancer molecular-based stratification was carried out by The Cancer Genome Atlas (TCGA) research network [58], which defines four molecular subtypes: *EBV-associated gastric cancers*, characterized by recurrent PIK3CA mutations, high levels of DNA hypermethylation, frequent JAK2 and CD274 (PD-L1) amplification and enrichment in genes involved in immune signalling; *MSI-high gastric cancer,* characterized by MLH1 silencing and consequent high levels of DNA hypermethylation; *genomically stable gastric cancer*, associated with a diffuse morphology and recurrent CDH1 and RHOA events; *gastric cancer with chromosomal instability* exhibiting a high number of TP53 mutations and amplifications of tyrosine kinase receptors. The prognostic and predictive value of TCGA four-tiered molecular classification has been highlighted: EBV-associated and MSI-high gastric cancers present the best prognostic features and may respond to targeted immunotherapies, chromosomal unstable tumors present a moderately poor prognosis but show sensitivity to chemotherapy, while genomically stable tumors show the worst prognosis and are resistant to chemotherapy [42,59].

There is partial correlation between histopathological and molecular classifications. EBV-associated gastric cancer shows the features of gastric cancer with lymphoid stroma (see below) in up to 80% of EBV+ cases (Fig. 6a); some cases present Crohn's disease-like lymphoid reaction, characterised by the presence of numerous lymphoid follicles with active germinal centres at the advancing edge of the tumor [60]; conventional-type histology, with scant lymphocytic infiltrate, is observed in a minority of cases. MSI-high gastric cancers may also present abundant intratumoral and peritumoral lymphocytic infiltrate. EBV infection and MSI-high status represent two alternative pathways of gastric carcinogenesis and mutually exclusive gastric

Table II. Kodama's Classification of growth patterns of early gastric cancer.

Growth Patterns	
Small mucosal (M)	Intramucosal EGCs measuring < 4 cm
Small mucosal (SM)	Intramucosal EGCs minimally invading submucosa measuring < 4 cm
Supermucosal (M)	Intramucosal EGCs measuring > 4 cm
Supermucosal, (SM)	Intramucosal EGCs minimally invading submucosa measuring > 4 cm
PEN (penetrating) (A)	EGCs massively invading submucosa with nodular pattern measuring < 4 cm
PEN (penetrating) (B)	EGCs massively invading submucosa with saw tooth pattern measuring < 4 cm

EGC: early gastric cancer

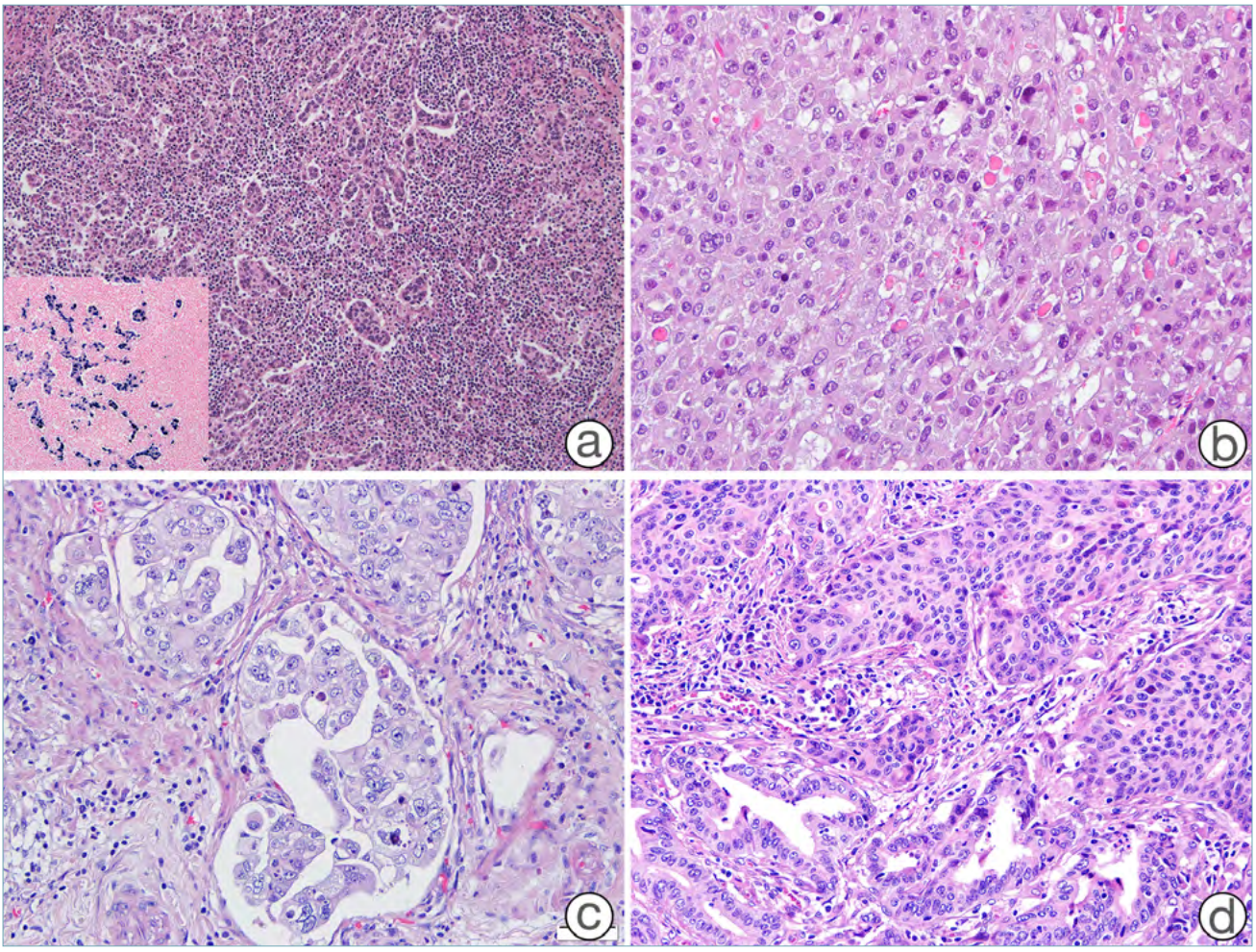

Figure 6. Rare histopathological variant of gastric cancer: (a) gastric cancer with lymphoid stroma showing abundant lymphoplasmacytic infiltrate (HE, magnification 10x); this case was associated to EBV infection, as evaluated by EBER-*in situ* hybridization (inset); (b) hepatoid gastric carcinoma with numerous hyaline globules (HE, magnification 20x); (c) micropapillary gastric carcinoma, with artefactual spaces at the periphery of the nests and inverted cell polarity (HE, 20x); (d) adenosquamous gastric carcinoma (HE, magnification 20x).

cancer molecular subtypes [61], with distinct transcriptional profiles, the former enriched by genes related in the immune response and the latter associated with mitosis and cell cycle biological terms [62]. Genomically stable gastric cancers show predominantly diffuse type histology [58]. When compared to pure signet ring cell carcinomas, poorly cohesive carcinomas classified as not otherwise specified show a distinct genomic profile, enriched by *TP53*, *RHOA*, *SMAD4*, *BRAF* and *PIK3CA* mutations [51]. Gastric cancers with chromosomal instability mostly present intestinal morphology [58].

Overall, tumor morphology may provide insight into tumor biology and should be used as a frame for the identification of clinically relevant subgroups, as the backbone for building algorithms for directed and cost-effective molecular characterization. Moreover, practical algorithms based on immunohistochemistry and in situ hybridization can be applied in the routine diagnostic practice to translate specific immunophenotypes into molecular subgroups with prognostic and predictive significance [63,64]. Thus, positive in situ hybridization for EBV-encoded small RNA (EBER) distinguishes EBV-associated gastric cancer; loss of expression of DNA mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) identifies most of gastric cancers with MSI-high status; genomically stable gastric cancers are identified by the poorly cohesive morphology and abnormal E-cadherin immunoreactivity

(decreased membranous, dotted, cytoplasmic, or absent); and p53 aberrant expression (overexpression or total loss) distinguishes a subset of chromosomal unstable gastric cancers with *TP53* activation [64].

Differential diagnosis

In poorly differentiated or undifferentiated gastric cancers, in which epithelial differentiation is not morphologically evident, pancytokeratin and EMA immunohistochemistry may highlight the epithelial nature of the neoplasm and distinguish it from aggressive lymphomas, metastatic melanoma, germ cell neoplasms or other malignant neoplasms with epithelioid morphology.

Very well differentiated gastric cancers should be distinguished from gastritis cystica profunda, a benign lesion characterised by the displacement of gastric foveolar epithelium, gastric glands and mucin into the gastric wall or serosa. Gastritis cystica profunda usually develops in stomachs subjected to traumatism (e.g. surgery, gastroenterostomy) as the result of chronic inflammation, direct injury and ischemia [65]. A helpful feature in distinguishing gastritis cystica profunda from adenocarcinoma is the presence of a rim of lamina propria-like stroma surrounding the cystically dilated glands, sometimes associated with smooth muscle fibres from the muscularis mucosae. Gastric adenocarcinoma may coexist with gastritis cystica profundal [66] and the distinction between the two lesions may be sometimes challenging (Fig. 7).

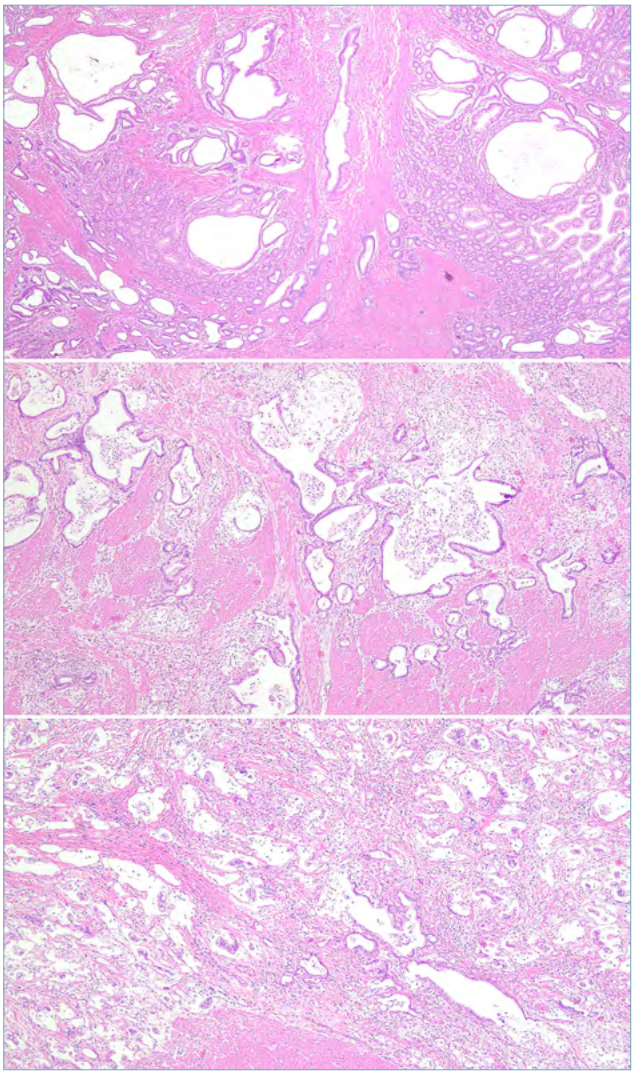

Figure 7. Gastric cancer arising in a stomach with *gastritis cystica profunda*: in *gastritis cystica profunda* gastric epithelium is displaced into the gastric wall (upper image, HE, magnification 4x); note the presence of *lamina propria*-like stroma surrounding the cystically dilated gastric glands; this case was associated to well differentiated tubular gastric adenocarcinoma (middle image, HE, 10x) with a mucinous component (bottom image, HE, magnification 10x).

Rare histotypes of gastric carcinoma

Uncommon histological variants account for about 5% of gastric cancer and according to the WHO 2019 classification of digestive system tumors [23], encompass i) squamous cell carcinoma; ii) adenosquamous carcinoma; iii) and undifferentiated carcinoma.

Squamous cell carcinoma of the stomach is a carcinoma with evidence of squamous cell differentiation, in the absence of other morphologic aspects. It is preferentially located in upper part of the stomach and is extremely rare, accounting for less than 0.1% of gastric cancers. Thorough tumor sampling is required to exclude the presence of other components. Potential pitfalls include metastases from a squamous cell carcinoma from another organs or extension from an esophageal squamous cancer. It is an aggressive disease, associated with poor patient prognosis.

Adenosquamous carcinoma of the stomach (Fig. 6d) is a malignant epithelial neoplasm composed of both squamous and adenocarcinomatous components. The squamous cell component should constitute at least a quarter of the whole neoplasm to render this diagnosis. It is extremely rare, accounting for 0.2% of all gastric cancers and preferentially affects males. It is predominantly located in the distal stomach. Immunohistochemistry for p40 may help confirm the presence of a morphologically suspected squamous cell component. Adenosquamous carcinoma is an aggressive neoplasm.

Gastric undifferentiated carcinoma has been recent-

ly recognized as a specific histotype of gastric cancer. It is an anaplastic carcinoma with no evidence of any type of tumor cell differentiation. Four subtypes are described, including i) large cell carcinoma with rhabdoid features, ii) pleomorphic carcinoma, iii) sarcomatoid carcinoma, and iv) carcinoma with osteoclast-like giant cells. Rhabdoid carcinomas account for about 6% of gastric cancers with a solid architecture. Undifferentiated carcinomas are usually large, fungating masses, composed of intermediate-to-large cells, often with pleomorphic elements. Pancytokeratin is usually expressed by neoplastic cells, while vimentin shows a characteristic perinuclear dot-like pattern of expression. A subset of such cancers exhibits loss of SMARCB1 (INI1) or SMARCA4 (BRG1) expression [67]. Mismatch repair protein deficiency may be present. Differential diagnoses include carcinomas with lymphoid stroma (a subtype of adenocarcinoma), lymphomas, sarcomas and melanomas. It is a very aggressive disease, with a dismal prognosis.

Carcinoma with lymphoid stroma (Fig. 6a) is also known as medullary carcinoma or lymphoepithelioma-like carcinoma. It is characterized by irregular sheets, trabeculae, poorly developed tubular structures and isolated cells, embedded within a prominent lymphocytic infiltrate with occasional lymphoid follicles. The lymphoid infiltrate can be so prominent that immunohistochemical study may be necessary to confirm the epithelial nature of the tumor. It is often associated with Epstein-Barr virus infection, which may be identified by *in situ* hybridization, though as a similar morphology can be observed in gastric cancer with microsatellite instability [68]. It is associated with a better prognosis in comparison with conventional adenocarcinoma.

Other types: *primary gastric hepatoid carcinoma* (composed by hepatocyte-like cells) (Fig. 6b), *adenocarcinoma with enteroblastic differentiation* (composed of clear cells arranged in tubulo-papillary structures) and *yolk-sac tumor-like carcinoma* share the immunohistochemical expression of alpha-fetoprotein and should be distinguished from a metastatic hepatocellular carcinoma or a germ cell neoplasm. Alpha-fetoprotein and primitive enterocyte differentiation biomarkers, such as SALL4, glypican-3 and claudin-6 are expressed in adenocarcinoma with enteroblastic differentiation and hepatoid gastric carcinoma [69,70]. Biomarkers which help to distinguish between primary hepatoid gastric adenocarcinoma from hepatocellular carcinoma metastases include SALL4 and claudin-6 expression in hepatoid gastric cancer and loss of SMARCB1 (INI1) immunoreactivity in hepatocellular carcinoma [71,72]. *Micropapillary carcinoma* (Fig. 6c), shows small aggregated of neoplastic cells without fibrovascular cores within empty clefts and is associated with a poor prognosis [73]. In this subtype, epithelial membrane antigen (EMA) and E-cadherin show a distinctive inside-out staining pattern with loss of immunoreactivity at the stroma interface. *Gastric adenocarcinoma of fundic-gland type* (chief cell predominant, parietal cell predominant, or mixed phenotype) account for about 1% of early gastric cancers and has been more frequently described in Asia [27]. It derives from the so-called oxyntic-type adenoma and shows immunoreactivity for pepsinogen I and MUC6, suggesting a predominant chief cell differentiation. This subtype is rather indolent, with a limited propensity to lymph node dissemination. Other types include *parietal cell carcinoma* and *Paneth cell carcinom*a and these are regarded as subtypes of gastric adenocarcinoma according to the 2019 WHO classification [23].

Hereditary gastric cancer syndromes

Three major hereditary autosomal dominant syndromes affecting the stomach have been described: hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and familial intestinal gastric cancer (FIGC) (Tab. III). Moreover, several other hereditary cancer syndromes are characterized by an increased risk of gastric cancer, namely classic and attenuated FAP, MUTYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Lynch Syndrome, Li-Fraumeni syndrome, hereditary breast and ovarian cancer syndrome, and Cowden syndrome [74].

Hereditary diffuse gastric cancer (HDGC)

Definition. HDGC is an autosomal dominant cancer syndrome defined by the presence of germline variants in *CDH1* or *CTNNA1* genes and characterized by increased risk of diffuse (poorly cohesive) gastric cancer and lobular breast cancer [75]. Families fulfilling genetic testing criteria for HDGC (Tab. III) but without *CDH1* or *CTNNA1* germline variants, should be defined as "HDGC-like" families [76].

Disease penetrance and clinical features. HDGC penetrance in proven mutation carriers is incomplete and variable between families [77]. According to recent estimates, the risk of DGC is 42% for males and 33% for females while the lifetime risk of lobular breast cancer ranges from 42 to 55% [76]. The time course from early to advanced HDGC is unpredictable [78] and prophylactic/risk reduction total gastrectomy in early adulthood is advised, regardless of endoscopic findings [76]. Indeed, appropriate endoscopic surveillance, also with advanced imaging endoscopy, fails to detect precursor or invasive

Table III. Hereditary syndromes affecting primarily the stomach.

Syndrome	Genetic testing criteria	Recommended genetic testing	Histopathological findings
HDGC	*Family criteria (first and second relatives)*: - At least 2 cases of GC in family regardless of age, with at least one diffuse GC - At least 1 case of diffuse GC any age and ≥1 case of LBC < 70 years in different family members - At least 2 cases of lobular breast cancer in family members < 50 years *Individual criteria*: - Diffuse GC < 50 years - Diffuse GC at any age in individuals of Māori ethnicity - Diffuse GC at any age in individuals with a personal or family history (1st degree) of cleft lip/cleft palate - History of diffuse GC and lobular breast cancer, both diagnosed < 70 years - Bilateral lobular breast cancer, diagnosed < 70 years - Gastric *in situ* signet ring cells and/or pagetoid spread of signet ring cells in individuals < 50 years	*CDH1* genetic analysis *CTNNA1* mutation analysis	Diffuse (poorly cohesive) GC and precursor lesions (*in situ* signet ring cell carcinoma, pagetoid spread of signet ring cells) LBC
GAPPS	*Essential criteria*: - Phenotypic features: proximal polyposis with antral sparing; no evidence of colorectal or duodenal polyposis; > 100 polyps carpeting the proximal stomach in the index patient or > 30 polyps in a first-degree relative of another patient; predominantly FGPs and/or fundic gland-like polyps - Proband or relative with either dysplastic FGPs or GC - Mutation in the promoter 1B (YY1 binding motif) of APC gene *Supportive criteria*: - Autosomal dominant patern of inheritance - Spectrum of other histological features, including hyperproliferative aberrant pits, hyperplastic polyps, gastric-type adenomas	*APC* promoter 1b mutation analysis	FGPs (with dysplasia) Hyperplastic polyps Hyperproliferative aberrant pits Intestinal and foveolar adenomas Mixed polyps with FGP-like, adenomatous and hyperplastic features Intestinal and mixed GC
FIGC	*IGCLC criteria in high incidence countries*: - Intestinal GC in three or more relatives; and - One being a first-degree relative of the other two; and - Two or more successive generations affected; and - Intestinal GC <50 years in one or more patients; and - Exclusion of gastric polyposis. *IGCLC criteria in low incidence countries*: - Intestinal GC in two or more first-degree relatives; - Intestinal GC in second-degree relatives, one diagnosed < 50 years - Intestinal GC in three or more relatives at any age. *Proposal of new criteria*: - GC in two or more relatives at any age; and - At least one intestinal GC	NA	Intestinal GC

FIGC, Familial Intestinal Gastric Cancer; **GAPPS**, Gastric Adenocarcinoma and Proximal Polyposis of the Stomach; **GC**, Gastric Cancer; **HDGC**, Hereditary Diffuse Gastric Cancer; **HNPCC**, Hereditary Non polyposis Colorectal cancer; **IGCLC**, International Gastric Cancer Linkage Consortium.

carcinoma foci in up to 80% of cases [79]. At the time of clinical presentation, almost the totality of affected individuals presents with advanced and incurable disease. In women, annual breast magnetic resonance imaging is advised, starting at 30 years of age [76].

Histopathological findings. Histopathological analysis of prophylactic (risk-reducing) total gastrectomies reveals, in the majority of the cases [80], multiple and tiny (< 0.1 mm to 16 mm) foci of intramucosal (pT1a) signet ring cell carcinoma [81] (Fig. 5c). Two intraepithelial precursor lesions (pTis) of signet ring cell carcinoma have been recognised exclusively in *CDH1* carriers, namely in situ SRCC, corresponding to the presence of signet ring cell within the basal membrane substituting normal epithelial cells, and pagetoid spread of signet ring cells, corresponding to a row of signet ring below the preserved epithelium of glands and foveolae, but still contained within the basal membrane [82]. A proportion of intramucosal carcinoma foci from *CDH1* carriers progress unpredictably to advanced disease, with diffuse infiltration of the gastric wall, peritoneal dissemination and metastases to distant organs. Ad-

vanced HDGC shows the features of poorly cohesive (diffuse) gastric cancer and is not distinguishable from the sporadic setting, except for the presence of multifocal intramucosal foci and precursor lesions in the mucosa distant from the tumor bulk [76]. In contrast to early HDGC, composed of bona fide signet ring cells with an "indolent" phenotype, advanced HDGC shows pleomorphic, bizarre and diffusely infiltrative neoplastic cells with increased proliferation and activation of oncogenic events [83,84]. The finding of "aggressive" histopathological features in endoscopic biopsy specimens from *CDH1* carriers is suggestive of advanced disease and should be reported in the pathology report to prompt staging and clinical intervention [78].

Immunohistochemical biomarkers. Consistent with biallelic inactivation of the *CDH1* gene and supporting the key role of E-cadherin loss for tumor initiation, E-cadherin expression is usually abnormal in precursor and invasive cancer *foci*. Diverse E-cadherin staining patterns have been described in HDGC, including complete loss of expression, reduced membranous immunoreactivity and "dotted" or cytoplasmic staining [83]. It should be clarified that HDGC may show retained E-cadherin immunoreactivity and that E-cadherin staining should not be used as a pre-screening method to select patients eligible for germline *CDH1* variant analysis.

Differential diagnosis. The pathology of HDGC is unique and diagnostic expertise is needed to provide high quality diagnoses, both in biopsies and in resection specimens. Specifically, criteria for the identification of signet ring cell lesions should be strictly followed in order to diminish the risk of over diagnosing nonspecific changes and mimics of signet ring cells, such as globoid transformation and vacuolization of the superficial epithelium, xanthomatous cells, and artefacts secondary to cell autolysis. Second opinion by an independent pathologist with experience in the field should always be sought.

In HDGC patients presenting both lobular breast cancer and diffuse gastric cancer, a metastatic tumor should be considered and can be morphologically indistinguishable [85]. Breast-associated immunomarkers are oestrogen receptor, BRST-2 (GCDFP-15) and mammaglobin, while the expression of CK20 and HNF4A may favour a diagnosis of gastric cancer [86].

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)

Definition. GAPPS is an autosomal dominant cancer predisposition syndrome associated with an increased risk of gastric cancer, arising in the context of polyposis of the proximal stomach. The genetic cause of GAPPS corresponds to germline point variants in the promoter 1B of the APC gene [87]. Accordingly, GAPPS is defined as a variant of FAP with an exclusive gastric phenotype. Diagnostic criteria for GAPPS are listed in Table III. To consider a diagnosis of GAPPS, the presence of polyposis elsewhere in the gastrointestinal tract should be ruled out.

Clinical features. GAPPS penetrance is also incomplete, as proven by the evidence of normal endoscopies in elderly obligate carriers [88]. The age of onset of gastric cancer is variable, ranging from 23 to 75 years. Fundic gland polyposis carpeting the gastric body and fundus has been detected as early as 10 years of age [88]. Recommendations on the management of GAPPS should be decided on a case-by-case basis. Clinical strategies encompass endoscopic surveillance with biopsies and/or polypectomies and prophylactic/risk-reduction gastrectomy [88].

Histopathological findings. GAPPS is characterized by multiple fundic gland polyps carpeting the gastric body and fundus, some of which show foveolar-type dysplasia and by the presence of hyperproliferative aberrant pits, corresponding to hyper-proliferative and disorganized oxyntic glands around gastric pits [89]. Other lesions include hyperplastic polyps, intestinal-type and foveolar-type adenomas with low- and high-grade dysplasia, as well as mixed polyps with FGP-like, adenomatous and hyperplastic features [89]. Gastric adenocarcinomas are intestinal-type or mixed-type [88].

Differential diagnosis. Prolonged therapy with proton-pump inhibitors could cause the development of multiple FGPs and sporadic fundic gland polyposis. According to the clinical criteria to consider GAPPS diagnosis (Tab. III), upper endoscopy should be repeated after discontinuation of therapy and appropriate off-treatment interval [88].

Familial intestinal gastric cancer (FIGC)

Definition. Familial intestinal gastric cancer (FIGC) is an autosomal dominant cancer syndrome associated with an increased risk of intestinal-type gastric cancer [90]. Diagnostic criteria (Tab. III) differ depending upon the incidence of gastric cancer in the population analysed. The genetic cause underlying the disease remains to be fully elucidated, although recent studies brought up the possibility of a distinctive polygenic cause for the disease [91].

Clinical features. The clinical phenotype of gastric cancer patients fulfilling the clinical criteria for FIGC has been characterized recently [91]. The lifetime risk of gastric cancer is 66% for both sexes and the mean age at diagnosis is 72 years, approximately 10 years earlier than patients with sporadic intestinal-type gastric cancers. The disease spectrum is broad, en-

compassing 18 cancer types including colorectal and breast cancer.
Histopathological findings. FIGC displays macroscopic and histopathological features that are undistinguishable from intestinal-type sporadic gastric cancer.

Post neo-adjuvant treatment tumor regression grade in gastric adenocarcinoma

Preoperative neo-adjuvant chemotherapy or combined radiotherapy and chemotherapy (neo-CRT) has become the standard approach for locally advanced gastric carcinomas. Pathological tumor regression grading (TRG) systems, which aim to evaluate and quantify the amount of residual tumor and/or regressive changes following neo-CRT, should be applied to all resections specimens.
TRG scoring permits prognostic stratification of tumors, indeed, complete pathological response is significantly associated with better outcome – at least in some series – and this classification into prognostic classes is the basis for personalized treatment and follow-up strategy.

Problems in TRG assignment

The presence of several validated classification systems for TRG has however led to some confusion as to which system should be preferentially applied. The presence of similar but not "exactly" similar TRG systems may, in part, explain why studies on the prognostic impact of response have yielded variable results [92]. There are many possible reasons which explain the lack of a universally accepted TRG system: 1) absence of standardized different sampling methods which could lead to over-diagnosis of complete pathological tumor regression and this may in part explain its variable prognostic impact. Indeed, the complete microscopic assessment of the entire ulcerated/scarring area should be performed and this is absolutely mandatory if no tumor is identified in the initial blocks; 2) not all classifications take into account the evaluation of response in loco-regional lymph nodes; 3) there is a relatively low concordance rate among pathologists in TRG assignment; 4) systems with a higher number of tiers (more than 4) do not offer any clear cut prognostic advantage [93].

TRG systems for Gastric Cancer

Gastric cancer specific TRG systems have been proposed starting from the 2003 Becker system [94] which requires the histologic assessment of the entire macroscopically identifiable residual tumor or the fibrous areas. The Becker system is based on the percentage of vital tumor tissue with no integrated nodal evaluation: TRG1 - complete tumor regression (TRG 1a: 0% residual tumor) or subtotal tumor regression (TRG 1b: < 10% residual tumor); TRG 2 - partial tumor regression (10% to 50% residual tumor); TRG 3 - minimal/no tumor regression per tumor bed (> 50% residual tumor cells with or without signs of tumor regression). Recently, an international group of experts, through a Delphi survey, has proposed a 4-tiered system based on the modified Becker grading system. The novelty of this system is the addition of the evaluation of response in metastatic lymph nodes (complete, partial, or no nodal response) and this seems add strength to the system [95].

Conclusions

The pathology report of gastric resections specimens requires a standardized approach as well as an in depth knowledge of prognostic and treatment associated factors. Furthermore, the recognition of hereditary conditions is important and requires cross-talk between the pathologist and clinicians.

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