Chapter 12

Malignant Gastric Tumours: The Role of Pathologist in the Diagnosis and for Therapeutic Decisions

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69838

Abstract

This chapter gives an overview about the most important malignant gastric tumours from the perspective of the pathologist. The first focus is the systematic classification of gastric carcinoma, neuroendocrine tumours, mesenchymal tumours and malignant lymphoma with related histomorphology-based and molecular-based diagnosis criteria including differential diagnosis pathologists have to consider when dealing with gastric tumours. The second focus addresses the issues of personalized therapy options in gastric tumours pathologists have to bear in mind. Currently, some subtypes of gastric adenocarcinomas have been proposed with therapeutic implications like microsatellite-instable carcinoma and checkpoint-inhibition or Her2/neu positive adenocarcinoma of intestinal-type and specific tyrosine-receptor blockade. Mesenchymal tumours are rare and can morphologically be quite variable. Mucosa-associated lymphoid tissue (MALT)-related marginal zone lymphoma is the most frequent gastric lymphoma but all other B-and T-cell lymphoma can occur in the stomach as well, and an exact subcharacterisation is very important due to different treatment decisions (e.g. eradication of helicobacter-pylori in MALT-lymphoma as first choice treatment vs. chemotherapy in Burkitt-lymphoma). Pathologists have to consider a large spectrum of differential diagnosis and conflicting immunohistochemical and molecular results. It will become more and more important to find out therapeutically relevant tumour subtypes and to use biomarkers to predict a successful individualized treatment.

Keywords: classification systems, diagnosis criteria, tumour subtyping, personalized treatment options

1. Introduction

The pathologist who deals with gastric tumours is responsible for the determination of the following factors:

- Dignity
- Main tumour differentiation (e.g. epithelial, mesenchymal, lymphatic)
- Treatment options
- Consider differential diagnosis (main differential diagnosis of gastric adenocarcinoma include neuroendocrine carcinoma, malignant lymphoma, metastasis of lobular breast carcinoma, epithelioid angiosarcoma or malignant melanoma)
- Morphology-based subtyping of gastric carcinoma (according to WHO or Lauren)
- Grading
- Staging (according to TNM-classification)
- Surgery resection status (R0-R2)
- Treatment relevant biomarkers: Her2/neu in gastric adenocarcinoma or in gastrointestinal stromal tumour (GIST), mutational analysis of c-kit or PDGFR)
- Regression scores after neoadjuvant treatment

Adenocarcinoma (including different subtypes) is the most common malignant gastric tumours of epithelial origin. In Western countries, declining incidence of gastric carcinoma is found; nevertheless, it remains the second most common cause of cancer-related death in the world [3]. In Germany, we expect about 9200 men and 6400 women with a newly diagnosed gastric carcinoma per year, and 70% of them will die carcinoma-related in the following 5

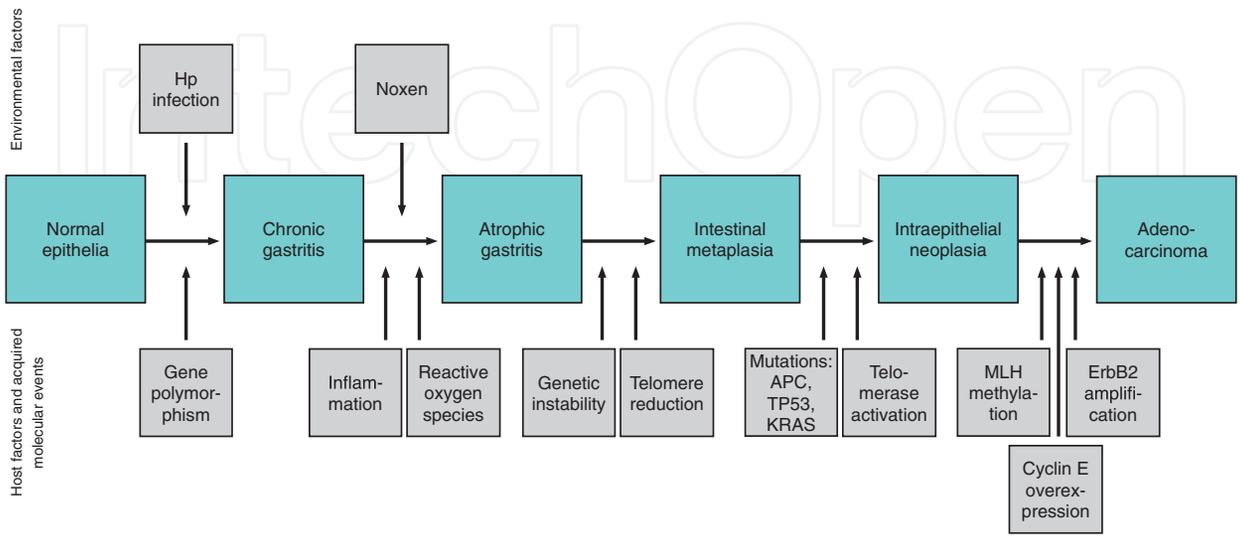

Figure 1. Pathogenesis of intestinal-type gastric adenocarcinoma.

http://dx.doi.org/10.5772/intechopen.69838

years. Particularly, if metastases/recurrences occur, the prognosis is still dismal with a median survival of 8 months (krebsdaten.de—Robert-Koch-Institut, Berlin 2015). Particularly, in Northern Europe and the United States, the distribution of carcinomas within the stomach changed in the past decades. The distal-located tumours (typically from the diffuse type of adenocarcinoma) are decreasing and the proximal tumours (typically from the intestinal type of adenocarcinoma) are increasing [1, 2].

From the pathophysiological point of view, main features of the intestinal type of gastric adenocarcinoma are (a) chronic inflammation of the mucosa (typically due to an infection of helicobacter pylori) with related mucosa damage and atrophy, (b) intraepithelial neoplasia and (c) fully invasive adenocarcinoma (**Figure 1**).

2. Classification of primary gastric carcinomas

In the past 90 years, there have been some different proposals for classification systems (**Table 1**). Especially in Western countries, the classification of Lauren (from 1965) and the current World Health Organisation (WHO) (from 2010) are accepted and of practical importance.

In general, gastric adenocarcinomas are built of (a) cohesive tumour cells forming tubular or papillary structures or (b) poorly cohesive (and often but not always) single carcinoma cells. It is not uncommon to see different growth pattern in the same tumour (morphology-based tumour heterogeneity).

2.1. WHO classification

The current WHO classification system describes four main subtypes of gastric adenocarcinoma and some rare entities [3].

2.1.1. Tubular adenocarcinoma

Cohesive tumour cells form slit-like, branching or someone dilated tubules or acinar structures. The individual carcinoma cells typically are columnar or cuboidal (**Figure 2A**).

2.1.2. Papillary adenocarcinoma

Papillary adenocarcinoma is usually a well-differentiated exophytic (finger-like) tumour. Fibrovascular tissue cores support the cohesive cylindrical or cuboidal tumour cells. Especially in superficial tumour biopsies, it is easy to miss an infiltrating growth pattern or desmoplastic stroma response (**Figure 2B**).

2.1.3. Mucinous adenocarcinoma

The main feature of this subtype is the dominance of extra-cellular mucinous pools—by definition, mucinous adenocarcinoma shows more than 50% extra-cellular mucin (**Figure 2C**). It is not uncommon to see some signet-ring cells scattered in the mucin.

WHO (2010)	Lauren (1965)	Goseki (1992)	Ming (1992)	Molecular (2014)
Papillary adenocarcinoma	Intestinal type		(Expanding type)	Chromosomal instable, MSI*
Tubular adenocarcinoma		Type 1 (type 2, type 3)	(Infiltrating type)	
Mucinous adenocarcinoma				
Signet-ring cell carcinoma	Diffuse type	type 4		Genomic stable
And other poorly cohesive carcinoma				
Mixed carcinoma	Indeterminate-type			
Adenosquamous carcinoma				
Squamous cell carcinoma				
Hepatoid adenocarcinoma				
Carcinoma with lymphoid stroma				EBV-related; MSI*
Choriocarcinoma				
Carcinosarcoma				
Parietal cell carcinoma				
Malignant rhabdoid tumour				
Mucoepidermoid carcinoma				
Paneth cell carcinoma				
Undifferentiated carcinoma				
Mixed adeno-neuroendocrine carcinoma				
Endodermal sinus tumour				
Embryonal carcinoma				
Pure gastric yolk sac tumour				
Oncocytic adenocarcinoma				

Notes: The correlation between the different classification systems is relative. The Ming classification cannot be assigned to the other classifications.
*MSI, microsatellite instable.

Table 1. Classification systems of adenocarcinoma.

2.1.4. Signet-ring cell and other poorly cohesive adenocarcinoma

Non-cohesive, isolated single tumour cells or carcinoma cells arranged in only small aggregates of few cells (**Figure 2D**).

Signet-ring cell carcinoma is composed of more than 50% signet-ring cells. The classic form of signet-ring cells is usually a single cell and has a central droplet of cytoplasmic mucin (optically clear in HE-staining). The atypical, hyperchromatic nucleus is eccentrically placed. Sometimes signet-ring cells can form lace-like glands.

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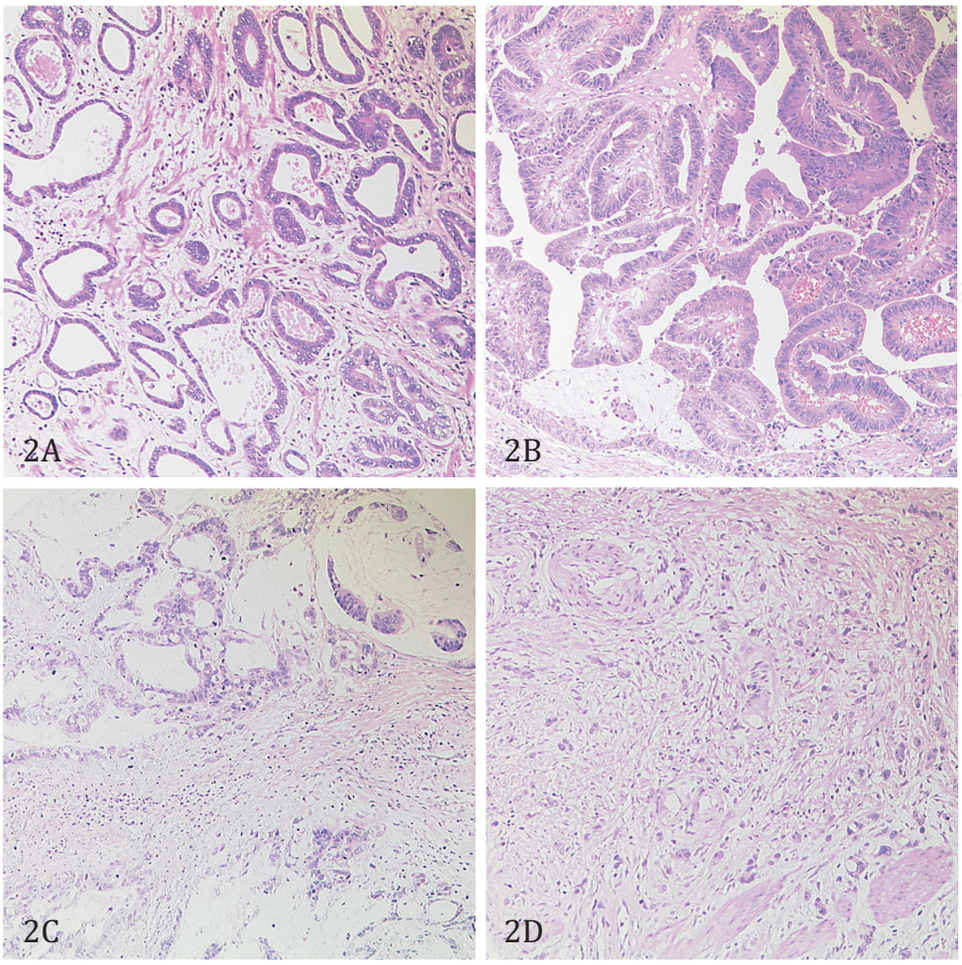

Figure 2. Four main histological subtypes of gastric adenocarcinoma (WHO): (A) tubular adenocarcinoma, (B) papillary adenocarcinoma, (C) mucinous adenocarcinoma and (D) poorly differentiated non-cohesive adenocarcinoma.

Other variants of poorly cohesive adenocarcinomas include (it is important to recognize that signet-ring cell carcinoma is just one subtype in the group of poorly cohesive adenocarcinoma): single cells with deeply eosinophilic cytoplasm, bizarre nuclei, histiocytic-like or accompanied with prominent lymphatic stroma.

2.1.5. Mixed adenocarcinoma

As described above, gastric carcinoma is highly heterogeneous (from the morphological as well as molecular point of view). The 'mixed' subtype is composed of different cohesive or poorly cohesive tumour components of the main four subtypes described above (for example tubular and signet-ring cell components). It is recommended to describe any histological component.

2.1.6. Rare carcinoma variants (to see all: compare **Table 1***)*

2.1.6.1. Adenocarcinoma with lymphoid stroma (lymphoepithelioma-like or medullary carcinoma)

Typically, poorly cohesive or vague tubular-forming tumour cells are associated with prominent lymphoid stroma. Often small lymphocytes are scattered between tumour cells. Poorly

cohesive tumour cells can be misinterpreted as lymphatic blasts. Typically, this subtype is EBV-related and it is easy to detect EBV-RNA using *in-situ*-test like EBER. Furthermore, carcinoma cells are often immunohistochemically strong PD-L1 positive. Nevertheless, not all EBV-related adenocarcinomas show the typical medullary morphological features. Some carcinomas of this subtype are microsatellite-instable easy and cost-effective detectable using immunohistochemistry for MLH1 (MSH2, MLH6 and PMS2). The loss of one (or more) of these DNA-repair proteins in tumour cell nuclei is in keeping with microsatellite-instability.

2.1.6.2. Squamous cell carcinoma

A pure gastric squamous cell carcinoma is very rare and is suspicious for a metastasis. Sometimes a mixed adeno-squamous cell carcinoma can be seen.

2.2. Classification according to Lauren (established 1965)

2.2.1. Intestinal type

Cohesive tumour cells form tubular, papillary or solid structures. The tumour typically shows well-demarcated pushing borders and it is associated with chronic gastritis (usually w Hp-infection) including intestinal metaplasia and pre-cancerogenous epithelial lesions like flat intraepithelial neoplasia/dysplasia. Abundant intracytoplasmic mucin production is not a feature.

2.2.2. Diffuse type

Poorly or non-cohesive tumour cells include signet-ring cells. The tumour typically shows infiltrating margins. Usually intestinal metaplasia of the gastric mucosa or classic dysplasia is absent. Probably a signet-ring cell carcinoma *in situ* develops from the proliferative foveolar zone and directly invades into the lamina propria.

2.2.3. Indeterminate type

Mix of intestinal type and diffuse type tumour cells.

2.3. Goseki classification (established 1992)

According to the degree of tubular differentiation and the amount of intracellular mucin, this classification separates four subtypes.

1. Tubular differentiation, mainly (just a few tumour cells with intracellular mucin allowed)
2. Tubular differentiation accompanied by abundant intracellular mucin
3. Minor components of both: few tubular differentiations and few intracellular mucin
4. Abundant intracellular mucin and no/very few tubular differentiation

http://dx.doi.org/10.5772/intechopen.69838

2.4. Ming classification (established 1997)

According to the infiltration zone, tumours with expanding, pushing border and tumours with infiltrating margins have separated. Types and architecture of tumour cells are not included.

1. Expanding type
2. Infiltrating type

2.5. Molecular subtypes

Most recently, molecular-based classification systems were introduced. According to the results of the cancer genome atlas research network [4], four subtypes exist (including their distribution):

1. Chromosomal instable (49.8%)
2. Microsatellite instable (21.7%)
3. Genomic stable (19.6%)
4. Epstein-Barr virus related (8.9%)

According to the results of Cristescu et al., four subtypes exist associated with distinct clinical outcomes [5].

1. Microsatellite stable TP53 inactivated
2. Microsatellite stable TP53 activated
3. Microsatellite stable with epithelial-mesenchymal-transposition (EMT)
4. Microsatellite instable

2.5.1. Clinical significance

Her2/neu (ERBB2) is a well-known receptor tyrosine kinase in breast carcinoma and currently, it is the only established therapeutically important tyrosine kinase in gastric adenocarcinoma. According to the results of the TOGA study, patients show a statistically significant benefit when using the Her2-specific tyrosine kinase inhibitor trastuzumab in Her2/neu positive gastric cancer. About 20% of gastric carcinomas are Her2/neu positive–most of them are located in the proximal part of the stomach and have an intestinal tumour differentiation. The role of the pathologists is the determination of the Her2-status on gastric carcinoma cells using immunohistochemistry or fluorescence-*in situ* (FISH). The criteria of Her2-positivity are different from that of breast carcinoma (compare **Table 2**).

	Gastric carcinoma	Breast carcinoma
Cut-off	Positive tumour cells biopsy: ≥5 cells resection: ≥10%	Positive tumour cells ≥10%
Pattern of expression	(Baso-)lateral expression sufficient	Circular expression required

Source: Modified according to Rüschoff et al. [6].

Table 2. Immunohistochemical Her2/neu criteria.

Gastric carcinomas are highly heterogeneous tumours and Her2/neu is usually not diffusely expressed in most of carcinoma cells (like it is commonly the case in breast carcinoma).

2.5.2. Molecular-based classification systems and prediction of treatment options

The molecular-based classification systems can be correlated to classical morphology-based divisions. The pathologist can use both to predict treatment options. The chromosomal instable/microsatellite stable subtype is more likely to belong to the intestinal type of adenocarcinoma or to the tubuloacinar-subtype and these tumours are more often correlated with a Her2/neu overexpression/amplification. The genomic stable/microsatellite stable with pithelial-mesenchymal-transposition (EMT) subtype is typically related to the diffuse type of adenocarcinoma or to the poorly cohesive adenocarcinoma including signet-ring cell carcinoma nearly never show Her2/neu positivity.

On the other hand, the microsatellite unstable or EBV-related subtypes can show different morphological patterns (sometimes associated with prominent lymphatic stroma) and are probably associated with better prognosis (Cristescu et al. described a better outcome in patients with microsatellite-instable tumours) and good treatment response to checkpoint-inhibitors (currently subject of clinical trials). In view of the above, pathologists should consider both traditional morphology-based and molecular-based classifications to find out the most reliable statement about prognosis and treatment options.

Cost-effective molecular-based classifications are possible using traditional morphology, immunohistochemistry (using antibodies against TP53, Her2/neu and MLH1) and *in-situ* technics (like EBER) [7, 8].

In surgical specimens, the determination of tumour stage is the most important prognostic factor in gastric carcinoma. In Western countries, the UICC-based TNM-classification system is well established (compare **Table 3**).

T	Primary tumour
T1	Tumour invades lamina propria, muscularis mucosae or submucosa
T1a	Tumour invades lamina propria or muscularis mucosa
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa
T4	Tumour perforates serosa or invades adjacent structures

T	Primary tumour
T4a	Tumour perforates serosa
T4b	Tumour invades adjacent structures
N	**Regional lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
M	**Distant metastasis**
M0	No distant metastasis
M1	Distant metastasis

Source: Modified according to Brierley et al [9].

Table 3. TNM classification.

The determination of tumour regression and estimation of the percentage of residual tumour after neoadjuvant chemo or radio-chemotherapy treatment is possible using standardized regression scores. Especially in Western countries, the regression score according to Becker et al. is well established (compare **Table 4**).

1a	No residual tumour (incl. treatment effect)
1b	<10% residual tumour (incl. treatment effect)
2	10–50% residual tumour (incl. treatment effect)
3	>50% residual tumour (incl. treatment effect)

Sources: Becker et al [10].

Table 4. Regression score.

3. Pre-cancerogenous epithelial lesions

3.1. Adenoma

Gastric adenomas are polypoid and typically solitary lesions. They commonly arise in a background of chronic atrophic gastritis with accompanied intestinal metaplasia. By definition, the epithelia of adenomas are neoplastic (intraepithelial neoplasia/dysplasia). Most of them show an intestinal differentiation (including goblet cells, Paneth cells) and look like a colon adenoma. According to the classification of colon adenoma, they can be subdivided into tubular, villous

or mixed adenomas and into low-grade or high-grade intraepithelial neoplasia. A minor group of gastric adenomas shows gastric gland differentiation like foveolar (so-called type II dysplasia) or pyloric gland differentiation, a mixture of foveolar/intestinal like differentiation or (very rare) a predominant Paneth-cell differentiation.

3.2. Pyloric gland-adenoma

Pyloric gland-adenoma usually arises in women and has a background of atrophic autoimmune-gastritis. This type of adenoma is polypoid and show closely packed pyloric gland-like tubuli. The epithelia are cuboidal with round nuclei and pale cytoplasm. Immunohistochemically pyloric gland-adenoma shows common gastric mucin (MUC 5A/C and MUC6).

3.2.1. Clinical significance

Adenomas must be removed with clear margins. Large adenomas (more than 2 cm) show a higher risk of malignancy.

3.3. Flat intraepithelial neoplasia

Especially in the stomach, intraepithelial neoplasia is flat and demonstrates endoscopically with only slight, uncharacteristic abnormalities. Frequently flat intraepithelial neoplasia arises in a background of chronic gastritis later in life (beyond the fifth decade). By convention, the intraepithelial neoplasia has to divide into either low grade or high grade.

Microscopically, the main characteristics of intraepithelial neoplasia consider cytology and architecture (like in adenoma):

Low-grade intraepithelial neoplasia preserves more or less the normal glandular differentiation, the epithelia show enlarged hyperchromatic nuclei, the nucleoli are not prominent, and cell pleomorphism and cell stratification are limited.

High-grade intraepithelial neoplasia demonstrates with crowding of glands, including budding and branching of some glands. The nucleoli are prominent and often intense eosinophilic.

3.3.1. Clinical significance

Flat low-grade intraepithelial neoplasia: re-endoscopy to exclude concurrent carcinoma is suggested. The risk of carcinoma is low (about 25%). Re-endoscopy twice a year and annual after two negative endoscopies is suggested.

Flat high-grade intraepithelial neoplasia: the risk of accompanied carcinoma is high (about 85%). An excision of the whole lesion/region is necessary [2, 11].

3.3.2. Vienna classification of gastrointestinal epithelial neoplasia

Geographic differences in interpretation of gastric epithelial tumours exist (generally between Western pathologists and Japanese pathologists). The Vienna classification of (pre-)cancerous lesions of the GI-tract tries to harmonize both interpretations (**Table 5**).

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Non-invasive high-grade neoplasia
4.1.	High-grade adenoma/dysplasia
4.2.	Non-invasive carcinoma (carcinom *in situ*)
4.3.	Suspicion of invasive carcinoma
Category 5	Invasive neoplasia
5.1.	Intramucosal carcinoma
5.2.	Submucosal carcinoma or beyond

Source: From Schlemper et al. [12].

Table 5. Vienna classification of gastrointestinal epithelial neoplasia.

4. Classification of neuroendocrine gastric tumours

According to WHO, tumours with neuroendocrine differentiation are separated into the following:

- well-differentiated neuroendocrine tumours (NETs) (grade 1 and grade 2)
- neuroendocrine carcinoma (NEC; subdivided into either small- and large-cell neuroendocrine carcinoma)

4.1. Neuroendocrine tumours (NETs)

NETs in total represent about 2% of all gastric malignancies.

Gastric neuroendocrine tumours (formerly 'carcinoid tumours') are mostly asymptomatic small 'polyps' on a background of hypergastrinemia-associated hyperplasia of endocrine cells in the gastric corpus of middle age adults (the 'classical' type 1 gastric NET, compare **Table 6**). But rarely they also can be associated with syndromes or unrelated to hypergastrinemia —these rare manifestations are usually correlated to unusual locations (e.g. antrum, more aggressive behaviour) [2, 16].

According to clinico-pathophysiological characteristics, three types of gastric NETs have been proposed (**Table 6**). These types share the same histological pattern. The great majority are tumours of enterochromaffin-like (ECL) cells induced by hypergastrinemia and caused by chronic atrophic corpus gastritis due to autoimmune gastritis and consecutive hypochlorhydria (type 1 NET) [3, 13, 17, 18].

Pathophysiologically, NETs start with ECL-cell hyperplasia (scattered or linear ECL-hyperplasia), which may confluent to micronodules. More than five micronodules in a group are called adenomatoid ECL-hyperplasia. Enlargement of adenomatoid ECL-hyperplasia with

	Type 1	Type 2	Type 3	Indicators of behaviour
Background mucosa	Chronic atrophic corpus gastritis—*usually autoimmune*	Hypertrophic with hyperplastic, intense eosinophilic parietal cells due to Zollinger-Ellison syndrome—*usually MEN1*	Normal (sporadic tumour)	Benign <1 cm mucosa or submucosa no angioinvasion
ECL-hyperplasia	Yes	Yes	No	Low-grade malignant beyond sumucosa angioinvasion >2 cm any endocrine functioning tumour Ki67 > 2–20%
Size	<1.5 cm multiple	<1.5 cm multiple > 1.5 cm in 20%	>1.5 cm, solitary rare < 1.5 cm multiple	High-grade malignant smaller or large cell neuroendocrine carcinoma Ki67 > 20%
Outcome	Never fatal	Rarely fatal	25% mortality	

Sources: Modified from Abraham et al. [13]; Capella et al. [14], and Klöppel et al. [15].

Table 6. Typing of gastric neuroendocrine tumours.

invasion and accompanied stroma reaction, the term dysplastic ECL-hyperplasia can be used. If the dysplastic ECL-nodules exceed 0.5 mm or invade the submucosa, the correct term is NET [2].

NETs of all types are composed of uniform cuboidal cells with round nuclei with stippled ('salt and pepper-like') chromatin and eosinophilic, granular cytoplasm. Nuclear pleomorphism, nucleoli and mitosis are unusual/infrequent in typical NETs (unlike neuroendocrine carcinoma). Growth pattern of NETs can be quite different and even quite heterogeneous in the same tumour forming nests, trabecular, tubules, rosettes or solid structures of tumour cells. Immunohistochemically, gastric NETs are consistent chromogranin A positive and have by definition a low Ki67 (up to 2%) [19, 20].

4.2. Neuroendocrine carcinomas (NECs)

Gastric neuroendocrine carcinomas are very rare (separated into small-cell and large-cell NECs). These poorly differentiated tumours are highly proliferative active (>20 mitosis/10 hpf or Ki67 >20%) and show an aggressive biological behaviour [3, 21].

Rare (atypical), NETs coexist with adenocarcinoma ('adenocarcinoid)—so-called MANEC (mixed adeno-neuroendocrine carcinoma, according to WHO). MANECs have the similar prognosis to that of conventional adenocarcinoma [2].

Clinical significance:

- NET, type 1: usually endoscopic polypectomy
- NET, type 2: usually endoscopic polypectomy
- NET, type 3: Surgery (e.g. gastrectomy); polypectomy in small tumours [2]

http://dx.doi.org/10.5772/intechopen.69838

5. Classification of malignant non-epithelial gastric tumours

5.1. Mesenchymal tumours

5.1.1. Gastrointestinal stromal tumour (GIST)

GISTs represent the great majority of mesenchymal tumour of the stomach and arise from the GI-pacemaker cells of Cajal; nearly all of gastric GISTs have a close contact to the gastric muscle wall (muscularis propria). Due to the wide morphological differences in the appearances of GIST: every mesenchymal tumour in the gastric wall is a GIST—until proven otherwise (compare differential diagnosis in Section 5.1.2.).

GISTs are usually tumours of adults with equal sex distribution but can affect children as well. Most of GISTs are solitary (rarely multiple) sporadic tumours but in some predisposing conditions like neurofibromatosis type 1, Carney-Stratakis syndrome (with paraganglioma and deficiency of succinate dehydrogenase) or associated with Carney triade (with extra-adrenal paraganglioma and pulmonary chondroma) tumours are more often multiple and show some other unusual features like epitheloid cell morphology or anatomical locations like oesophagus (compare **Table 7**) [22–28].

GISTs vary in size from very small only incidentally identified to very large bulky tumours. Particularly, the large tumours demonstrate with cysts, haemorrhage or necrosis. The histomorphology appearance is quite variable. Most GISTs show whorls, bundles or fascicle of monotonous spindle-cells with blunt-ended nuclei and eosinophilic cytoplasm (similar to tumours with muscle differentiation, compare **Figure 3**). Pleomorphism of tumour cells is not a typical feature (nevertheless some tumours can show striking pleomorphic nuclei). Sometimes paranuclear clear vacuoles or GISTs with small and intense eosinophilc homogenous filamentous material between tumour cells (skeinoid fibres; but usually seen in GIST of the small bowl) are seen. Some GISTs have an epitheloid cell appearance and these tumours are more often immunohistochemically CD117 negative. DOG1 ('discovered on GIST') is currently the protein with the highest sensitivity and specificity for GIST and is consistently positive in all epitheloid GISTs as well (compare **Tables 7** and **8**) [23, 29, 30].

The molecular basis for the CD117 protein-overexpression is an activating mutation of the c-kit gene (usually in the exons 9 or 11). A few tumours have mutations in platelet-derived growth factor receptor, alpha (PDGFRa), only.

Different mutations show different sensitivity to drug-related CD117 blockade (compare **Table 9**) [31]. Therefore, it is important to settle the exact underlying mutation.

Average age	60	40–50	<35	<25	50
Sex	1:1	1:1	w > m	1:1	1:1
Assoc. symptoms	None	Hyperpigmentation, Mastocytosis Urticaria	Extrarenal Paragan-glioma Chondroma	Extrarenal Paragan-glioma	Neurofibroma Cafe-au-lait

Source: Modified according to Agarwal et al. [28].

Table 7. Clinico-pathological characteristics in GIST.

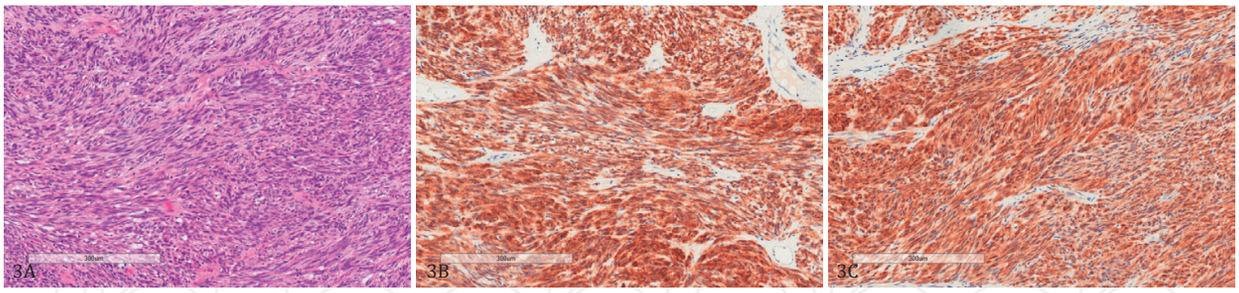

Figure 3. Spindle cell GIST (c-kit and DOG1 immunohistochemistry): (A) spindle cell GIST (HE), (B) DOG1 and (C) CD117.

Antibody	% of cases	Remarks
CD117(=c-kit)	90	Membrane staining; sometimes paranuclear dot; can be negative mainly in epitheloid GIST
DOG-1	≈100	Highest sensitivity and specificity
CD34	80	Low specificity
Vimentin	≈100	Very poor specificity; leiomyoma are negative for 'Vimentin'
SMA +h-Caldesmon	30	
Desmin	<5	Most GIST are completely negative, sometimes patchy
S100	1–5	Focally
MelanA	<1	Mainly in epitheloid GIST; DD: epitheloid PEComa

Table 8. Immunohistochemical markers in GIST.

Imatinib dosage in dependence of c-kit/PDGFRA-genotype	
Genotype	**Imatinib dosage per day**
c-kit Exon 11, 13, 17, wildtype	400 mg
c-kit Exon 9	800 mg
PDGFR-α-wild-type, Exon 12, 14	400 mg
PDGFR-α Exon 18 (D842V) mutation	Imatinib resistant
Source: Modified from onkopedia; GIST.	

Table 9. Imatinib dosage.

It is important to realize that all GISTs have the potential to metastasize. But most gastric GISTs follow a benign biological behaviour. The most important tumour characteristics associated with risk of progression are size, mitotic rate and anatomical location (but here we discuss gastric GIST, only) (compare **Tables 9** and **10**).

Risk of progression	Size (cm)	Mitotic activity (per 50 hpf*)
None	<2%	<5
1.9%	>2 to ≤5	<5
3.6%	>5 to ≤10	≤5
	≤2	≥5
10%	>10	≤5
16%	>2 to ≤5	>5
55%	>5 to ≤10	>5
86%	>10	>5

*high power field
Source: Modified from: Miettinen et al. [32].

Table 10. Risk of progression of gastric GIST.

5.1.2. Main differential diagnosis to GIST (including typical immunohistochemical/molecular findings)

- Leiomyoma/leiomyosarcoma—h-caldesmon, desmin
- Leiomyoma: usually small and related to muscularis mucosae. Very rare leiomyoma exist in the deeper gastric wall (usually located in the proximal part of the stomach). Diffuse positive for desmin, negative for dog1, CD117 (scattered mast cells between tumour cells are CD117 positive; mast-cell–rich leiomyoma can be challenging) and Vimentin
- Leiomyosarcoma: rare. Can look quite similar. Usually has much more cell pleomorphism
- Schwannoma—S100 and rim of lymphocytes in periphery of tumour
- Desmoid fibromatosis—ß-catenin nuclear expression
- Rhabdomyoma or rhabdomyosarcoma: Desmin, myogenin, MyoD1
- Haemangioma—ERG, CD31
- Calcifying fibrous tumour: paucillar, dense collagen, psammomatous calcification, patchy lymphocytes—factor XIIIa (in GI-tract usually adults, in soft tissue: usually children)
- Inflammatory fibroid polyp—CD34, PDGFRa
- Inflammatory myofibroblastic tumour—ALk1
- Solitary fibrous tumour (SFT)—STAT6
- Synovial sarcoma—TLE1
- Liposarcoma (well-/dedifferentiated or myxoid/roundcell)—mdm2 or FUS-CHOP-translocation
- Angiosarcoma (including: Kaposi-Sarcoma): ERG, CD31 (CAVE: macrophages)
- Clear cell sarcoma-like (malignant GI-neuroectodermal tumour): S100 (EWSR1 translocation)
- Glomustumour: SMA

- Gastroblastoma: benigne bi-phasic tumour in children. Epithelial component can be positive for CD117, mesenchymal component CD10 positive
- Granularcelltumour: S100
- Plexiform fibromyxoma: SMA, CD10 (very rare; multinodular, myxoid stroma, paucicellular, no atypia, prominent capillary network, just few mitosis, typically in wall of stomach)

5.2. Malignant lymphoma

5.2.1. Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)

The great majority of gastric malignant lymphoma in Western countries belongs to the mucosa-associated lymphoid tissue (MALT) subtype. About 70–80% of MALT-lymphomas are associated with a chronic helicobacter pylori (Hp) infection. The Hp-infection is one of the main drivers of this type of lymphoma; eradication of Hp is the first choice of treatment and induces a regression of the MALT-lymphoma in about 75% of cases. Hp-negative MALT-lymphoma can be associated with some other infections (like Hepatitis C) or are related to immunosuppression (due to AIDS or post-transplant) or some autoimmune diseases. Prognosis is mainly related to stage (Ann Arbor staging). Gastric MALT lymphoma occurs frequently multifocal. It is noteworthy that some gastric MALT lymphoma can affect other MALT-bearing organs like gut, salivary glands and bronchial [2, 33].

Endoscopically, (MALT)-lymphoma imitates carcinoma (including mucosa-ulceration) and is usually located in distal parts of the stomach. Sometimes non-characteristic gastritis-like or nodular appearance dominates.

Histologically, MALT-lymphoma shows the characteristics of other marginal zone lymphomas like dense infiltrations of small to intermediate-sized more or less monomorphic lymphoid cells with clear cytoplasm. Some tumours show a striking plasmacytoid-like differentiation. Lympho-epithelial lesions (destruction of epithelial components of the mucosa) are highly characteristic for this type of lymphoma. Scattered blasts are typical [34, 35].

Immunohistochemically, MALT-lymphomas are positive for CD20 and half each for CD43. Negative for CD10, cyclin D1, CD5, CD23.

5.2.1.1. Clinical significance

Hp-eradication is the first choice of treatment (independent of Hp status at the surrounding mucosa). But tumours with nuclear BCL10 expression and positive translocation t (11;18) (q21;q21)) fail to response to Hp-eradication. This subtype is associated with a low risk of progression into an aggressive B-cell-lymphoma [36–38].

All other B- and T-cell-lymphomas and some other rare differential diagnosis can primary occur in the stomach, but are frequently an expression of a secondary infiltration (compare Sections 5.2.2–5.2.4) [39].

5.2.2. Small cell B-cell-lymphoma

- Follicular lymphoma (grade1/2): CD10, BCL6, HGAL
- Mantle cell lymphoma: CD5, Cyclin D1 (due to translocation t(11;14), Sox11
- Lymphocytic lymphoma: CD23, CD5

5.2.3. High-grade B-cell-lymphoma

- Diffuse large B-cell-lymphoma: CD20, CD79a, Mum1, BCL2 positive. Some MALT-lymphomas show a transformation into an aggressive large B-cell-lymphoma.
- Burkitt-lymphoma: CD20, CD79a, BCL2 negative, CD10 positive. C-Myc translocation by FISH.

5.2.4. Others

- Primary solitary gastric plasmacytoma
- T-cell-lymphoma
- Langerhans cell histiocytosis, myeloid leukaemia

6. Metastasis

About 2.6% of all gastric tumours are metastases to the stomach.

Malignant melanoma is the most frequent reason for metastases followed by some carcinoma: like lobular breast carcinoma (compare **Figure 4**) or colon, prostate, lung, pancreas, liver (mainly hepatocellular carcinoma) and very rare sarcoma (epithelioid angiosarcoma) [40–43].

The correct diagnosis can be quite challengingly—the following immunohistochemistry panel may help to find the correct answer:

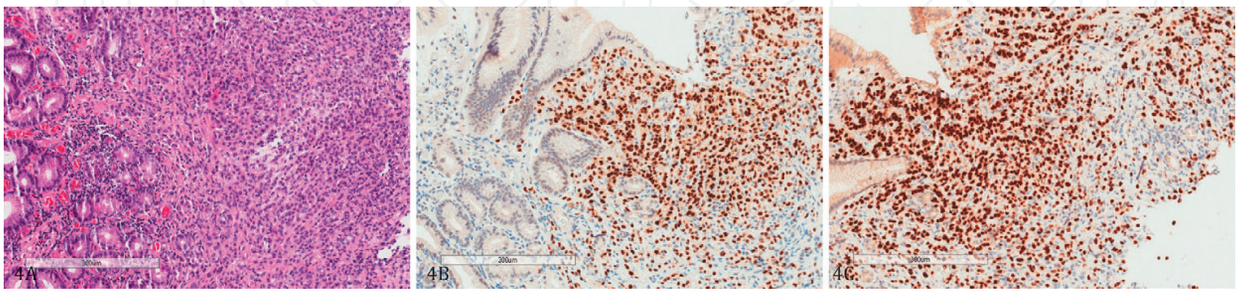

Figure 4. Metastasis lobular breast carcinoma: (A) metastasis lobular breast carcinoma (HE), (B) estrogen-receptor and (C) GATA3.

- AE1/AE3, GATA3, estrogen-receptor (progesterone -receptor, GCDFP): breast
- SOX10 (HMB45, MelanA, MITF): malignant melanoma
- SATB2, CDX2: colon
- Androgen-receptor (PSMA, NKX3.1, ERG): prostate

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