Chapter 2
Histopathology of Early Mucosal Neoplasias: Morphologic Carcinogenesis in the GI Tract

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2.1 Introduction

Early cancer suggests carcinoma curable with resection – a clinical concept coined in Japan – and more and more defined by macroscopic and microscopic criteria over the years throughout the gastrointestinal tract [1–3]. In general, it is applied to mucosal cancers without or with minor submucosal invasion, with a low probability of lymph node metastasis and >90 % rate of cure by R0 resection.

In Japanese tradition, endoscopic features have been correlated with histopathological findings. Mucosal surface alterations of well-differentiated cancers and precursor lesions as compared to non-neoplastic mucosa have been characterised by histology in parallel with stereomicroscopic observation and image-enhanced endoscopy (IEE). Well-differentiated early mucosal neoplasias, e.g. in the colon, revealed distinct margins and typical alterations of epithelial surface and mucosal capillary structure [4, 5]. In addition, several morphological pathways of carcinogenesis exist in each organ such as colon, stomach, or oesophagus [4, 6–9], and therefore, the endoscopist must be familiar with different early cancerous lesions and their precursors.

Western and Japanese classifications differed in the criteria for intraepithelial high-grade dysplasia vs. mucosal cancer [10, 11]. This has been largely resolved by the consensus Vienna classification of gastrointestinal epithelial neoplasias [12] extended in Paris by the macroscopic and microscopic International Classification which is based on Japanese criteria [6]. Early cancers and precursor lesions in the gastrointestinal tract are best defined with these classifications.

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Table 2.1 Vienna classification of gastrointestinal epithelial neoplasia [12]

Category	Description	Japanese viewpoint
Category 1	Negative for neoplasia/dysplasia	[a]
Category 2	Indefinite for neoplasia/dysplasia	[a]
Category 3	Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)	[a]
Category 4	Non-invasive high-grade neoplasia	
	4.1 High-grade adenoma/dysplasia	Non-invasive carcinoma[c]
	4.2 Non-invasive carcinoma (carcinoma in situ)[b]	
	4.3 Suspicion of invasive carcinoma	[a]
Category 5	Invasive neoplasia	
	5.1 Intramucosal carcinoma[d]	[a]
	5.2 Submucosal carcinoma or beyond	[a]

[a]Identical
[b]Non-invasive indicates the absence of evident invasion
[c]High-grade adenoma/dysplasia could be regarded as non-invasive carcinoma according the Japanese criteria of atypia
[d]Intramucosal indicates invasion into the lamina propria or muscularis mucosae.

2.1.1 Paris Classification and Malignant Potential of Neoplasms

2.1.1.1 Classification of Malignant Mucosal Neoplasms

The International Classification (for macroscopic types, see Fig. 4.4) is based on the histopathological definitions agreed upon in the Vienna classification (Table 2.1). There is still some disagreement between Japanese and Western pathologists as to the categorisation of lesions into high-grade intraepithelial neoplasias (HGIN) or definite cancer in situ (T0m1), because diagnostic criteria of cancer are based more on biopsy-proven tumour invasion into the lamina propria of the mucosa in the West, but more on atypias (nuclear features and intraepithelial gland structure) similar to the intraepithelial spreading component of invasive carcinomas in Japan (Table 2.2). Therefore, up to 50 % of carcinomas in situ diagnosed in Japan may be categorised HGIN in the West [10, 11]. However, Japanese pathologists better predicted from single biopsies the correct categorisation of the entire en bloc resected neoplasias, because the majority of HGIN in the stomach were definite cancers in the resected specimens [11]. For the decision whether an early malignant lesion should be resected en bloc, this difference is irrelevant, since both HGIN and carcinoma in situ should be removed en bloc [1, 3, 6]. Minor differences may also exist in the categorisation of low- vs. high-grade intraepithelial neoplasias (LGIN vs. HGIN), but this decision is primarily a matter of individual expertise and should involve an expert reference pathologist [3, 6, 10].

Table 2.2 Japanese criteria for diagnosis of colorectal adenomas and differentiated cancers [13]

				Well-differentiated adenocarcinoma	
Criteria of atypia		Normal	Adenoma	Low grade	High grade
Cellular atypia	Nuclear size (μm)	4.5×1.5	→	→	≤20×10
	Chromatin (blue-violet)	Dotted	→	→	Coarse, bright
	Nuclear polarity	Basal	→	→	Nonpolarised
	Nucleus/gland ratio	Low	→	→	High
	Nucleus/cell ratio	0.15–0.3	→	→	0.5–0.9
Structural atypia	Glandular structure	Tubular	Tubular/villous ± branching	Tubulovillous, ± snaking, branching	Tubulovillous and cribriform
	Index of structural atypia	Normal	→	→ Increased	

2.1.1.2 Malignant Potential

The likelihood of nodal metastasis mainly depends on *histologic grading* and *depth of submucosal invasion* of any T1 carcinoma as well as on *macroscopic type* and *anatomical localisation* in the gastrointestinal tract.

Well-differentiated mucosal cancer shows a relatively structured and continuous infiltrative growth pattern of glandular crowding, branching, and budding with clear histologic borders to normal localised tissue being reflected by clear endoscopic margins of the neoplasia. Relative loss of polar structure of epithelial cell layers, enhanced nucleus/cytoplasm ratio, and bulky growth of epithelial cell layer in the neoplasm (as compared to normal epithelium and mucosa) alter the surface aspect of mucosal neoplasias – inducing a mucosal pattern most often visible on IEE. In case of massive submucosal invasion of coherently growing carcinoma, the surface gland structure (typical for differentiated mucosal cancer) becomes destroyed – yielding highly irregular or even non-structured surface (amorphous pattern) on stereomicroscopic observation as well as on IEE. In addition, differentiated mucosal cancers require neoangiogenesis for deep submucosal invasion – showing on IEE irregular microvessels in mucosal proper layer as demonstrated by immunohistochemistry in resected early cancers and correlated with imaging features on IEE [1, 3, 5, 14].

Likelihood of lymph node metastasis generally increases with *depth of invasion* of well-differentiated early cancer [2, 3, 15]. The best data on these correlations have been collected in large surgical series of resected early cancers with dissection of regional lymph nodes [2, 15–21], as summarised in Table 2.3. To predict risk of metastasis to locoregional lymph nodes for well-differentiated early cancers, T1 lesions of the colon are categorised into "low risk", i.e. grading G1 or G2, no invasion of lymphatic vessels (L0) or submucosal veins (V0), and submucosal extension of less than 1,000 μm, vs. "high risk" in the presence of any feature like tumour budding (isolated tumour cells at the invasive tumour front), submucosal invasion ≥1,000 μm, lymphatic or venous vascular invasion, or grading G3 or G4 [15].

Table 2.3 Probability of lymph node metastasis of superficial cancers by extent of submucosal invasion (μm)

Carcinoma	Depth of invasion	LN pos. cases (%)
Oesophagus [3, 16, 18, 20, 21]		
SCC (*type 0–II; grading G1, G2*)	m1	0 %
if *L0, V0, d <5 cm, no ulcer, cN0*	m3 (muscularis mucosae)	8 %
	sm1 (<200 μm and d <5 cm)	4.2 %
Overall	sm1 (<200 μm)	17 %
AC (CLE Barrett's)	pT1m	1.9 % (CI 1.2–2.7 %)
	pT1sm	21 %
Stomach (*if L0, V0*) [2, 17]		
AC intestinal type G1–G2	pT1m (d <30 mm)	0 % (CI 0–0.3 %)
	pT1sm1 (<500 μm)	0 % (CI 0–2.5 %)
AC undifferentiated G3–G4	pT1m (d <20 mm, no ulcer)	<1 % (CI 0–2.6 %)
Colon [1, 19] (if *G1 or G2, L0, V0*)		
AC type 0–II	pT1 (sm <1,000 μm)	1.4 % (0–5 %)
AC type Ip	pT1 (Ip-head, sm < 3,000 μm)	0 %

The *macroscopic type* (Paris classification, Fig. 4.2) is another indicator of risk of lymphatic and/or vascular spread of early cancer [1–4, 15], probably reflecting heterogenous morphogenic and molecular pathways of oncogenesis (compare Sect. 2.2 on pathways of colonic carcinogenesis).

Poorly or undifferentiated early cancers (G3/G4) show loss of cell–cell adhesion, discontinuous growth pattern, high nucleus/cytoplasm ratio paralleled by more rapid tumour cell replication/proliferation, and higher metastatic potential (e.g. anoikis) on a cell biology level. Therefore, lymphatic vessel or blood vessel permeation is frequent with even small, poorly differentiated intraepithelial early cancer, and so are higher rates of lymph node (or haematogenous) metastases as compared with well-differentiated mucosal cancer [2, 15, 17]. The risk of metastatic spread to locoregional lymph nodes is increased for poorly differentiated early gastric cancer exceeding lateral extension of 20 mm [2, 17]. Also, margins of undifferentiated mucosal cancers tend to be less clear, the epithelial surface structure in the central part of the cancer may be destroyed by epithelial invasion with undifferentiated cancer cells, and the microcapillary pattern in the lamina propria mucosae tends to be very irregular on magnifying NBI endoscopy.

Based on extensive quantitative *histopathologic analysis* of surgical resection specimens of early gastrointestinal cancers, the *likelihood of cure* from early cancer achievable by endoscopic en bloc resection with free margins can now be predicted on based histologic characteristics, lateral size, depth of submucosal invasion, absence of lymphovascular invasion, and organ location in the GI tract (Table 2.4 Criteria of *curative resection*). Magnifying endoscopic analysis of early cancers attempts to predict from characteristic alterations of the macroscopic type, surface and microvascular structure, whether the lesion allows endoscopic resection en bloc for cure (*Indication criteria*, see Chaps. 3 and 6–10).

Table 2.4 Criteria of *curative endoscopic resection* in oesophagus, stomach, and colorectum

Organ	Criteria of curative resection en bloc
A. Stomach	1. *Guideline criteria*
	m-ca, diff. type, ly (–), v (–), Ul (–), and ≤2 cm in size
	2. *Expanded criteria*
	m-ca, diff. type, ly (–), v (–), Ul (–), and any size >2 cm
	m-ca, diff. type, ly (–), v (–), Ul (+), and ≤3 cm in size
	sm 1-ca (invasion depth <500 μm), diff. type, ly (–), v (–)
	m-ca, undifferentiated type (G3), ly (–), v (–), Ul (–), and size <2 cm
B. Oesophagus (squamous lesions only)	1. *Guideline criteria*
	1) pT1a-EP-ca, 2) pT1a-LPM-ca
	2. *Expanded criteria*
	pT1a-MM-ca, ly (–), v (–), diff. type, expansive growth, ly (–), v (–)
	cT1b/sm-ca (invasion depth <200 μm), ly (–), v (–), infiltrative growth pattern, expansive, diff. type, ly (–), v (–)
C. Colorectum	1. *Guideline criteria*
	m-ca, diff. type, ly (–), v (–)
	sm-ca (<1,000 μm), diff. type, ly (–), v (–)

Modified from Toyonaga et al. [22]
m mucosal, *ca* cancer, *diff* differentiated, *ly* lymphatic invasion, *v* vascular invasion, *Ul* ulceration, *sm* submucosal, *EP* epithelium, *LPM* lamina propria mucosae, *MM* muscularis mucosae

2.2 Characteristics of Colonic Neoplastic Lesions

On colonoscopy, most protruded or flat lesions classify as adenomatous or hyperplastic according to histomorphology – see Fig. 2.1. Whereas strictly hyperplastic lesions are non-neoplastic, the similarly looking serrated adenomas are – like polypoid adenomas – cancer precursor lesions.

The usual perception of morphological carcinogenesis still focusses on the classical "polyp–cancer sequence" [23], although at least four other precursor–cancer pathways exist in the colon – the depressed neoplasia pathway, non-polyposis (HNPCC) pathway, serrated adenoma pathway, and in ulcerative colitis and in colitis Crohn the "inflammation–dysplasia (DALM)–carcinoma pathway" [1, 4, 7, 23–27] (Table 2.5).

2.2.1 Classical Polypoid Adenoma–Carcinoma Pathway

Polyps have been snared in the colon since 1972, and histologic observations led to the polypous adenoma–dysplasia–cancer sequence [29] that had been translated into molecular pathways of oncogenesis by Vogelstein et al. [23]. In addition, screening colonoscopy with clearing of all detectable adenomas by endoscopic polypectomy had reduced the incidence of CRC far below predicted rates [30]. This served as rationale for the approval of colonoscopy screening to prevent

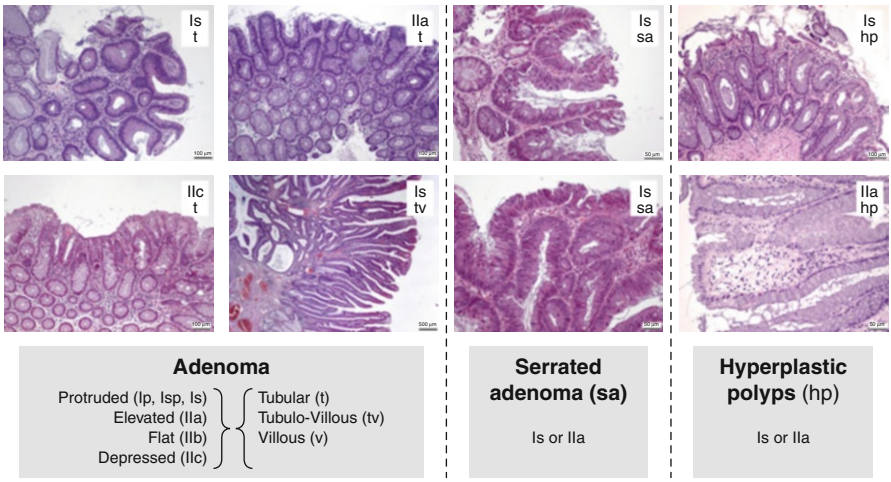

Fig. 2.1 Principles of histomorphology of adenomatous or hyperplastic mucosal lesions in the colon

Table 2.5 Morphogenic pathways of colorectal carcinogenesis

Superficial neoplasms	CRC risk estimates	Precursors of CRC (estimated)
1. Classical adenoma		
Polypoid (type 0–Ip,s)		
Distal > proximal	10 years	
CIN (LoH, kRAS, APC)	15–30 %	60 %
2. Serrated adenoma		
Serrated polyp (kRAS), distal	5 years	
Sessile SA (BRAF), proximal	60 %	~10 %
CIN (kRAS)		
MSI+++ (BRAF, CIMP)		
3. Depressed NpI 0–IIc	1–<5 years	25–30 %
"De novo cancer"	75 %	
Proximal > distal		
MSI+++		
4. HNPCC adenoma		
Flat adenoma 0–IIa/b/c	1–5 years	~5 %
Proximal (70 %) > total colon	40–80 %	
MSI+++ (MLH mut, CIMP)		

According to refs. [1, 4, 6, 7, 26, 28]

CRC in the USA and many Western countries. From an endoscopic vantage point, Kudo et al. [4] and Uraoka et al. [31] described a separate entity – superficially spreading adenomas of more than 10 mm diameter – as lateral spreading type neoplasias (LST) which require an ablative strategy of its own.

2.2.2 Flat/Depressed Colonic Adenoma–Carcinoma Pathway

The majority of advanced CRC may develop from a non-polypoid precursor lesion [1, 4, 32, 33]. In the "depressed neoplasia–carcinoma sequence", minute "de novo" cancers of 2–5 mm size, most with submucosal invasion, have been described by Shimoda et al. [33]. In more than 1,000 colonic neoplasms, they diagnosed 71 cancers, and 78 % of these originated from non-polypoid precursor lesions and 22 % from polypoid adenomas. Ten of 75 cancers were minute (<5 mm) depressed-type cancers without adenomatous areas, but all of them with submucosal invasion. Depressed-type (0–IIc) colorectal carcinomas are at a more advanced stage than non-depressed lesions (0–IIa or b) [4, 6]. Therefore, these depressed-type neoplasms have a high likelihood of malignant progression and tend to show shorter evolution time to cancer.

2.2.3 Serrated Adenoma–Carcinoma Pathway

Sessile serrated adenomas show the endoscopic appearance and pit pattern (type II) of hyperplastic polyps, whereas polypoid (i.e. "traditional") serrated adenomas mainly exhibit adenomatous pit pattern (pp IIIL or IV) [26, 32]. However, these lesions are premalignant via the "serrated pathway" to adenocarcinoma [7, 25, 26, 32, 34]. About 8 % of all and 18 % of proximal colorectal carcinomas originate from the "serrated pathway" involving the sequence hyperplastic aberrant crypt foci → hyperplastic polyps (HP) or sessile/polypoid serrated adenomas (SSA/TSA) → admixed polyps (serrated adenoma with dysplastic focus) → cancer [32]. Sessile serrated adenomas are located mainly in the proximal colon, traditional polypoid serrated adenomas more often (>60 %) in the left hemicolon [26, 32]. Serrated adenomas show about twice as frequent malignant transition than classical polypoid adenomas. On a molecular basis, serrated polyps are the precursors of type 1-CRC (CIMP-high/MSI-high/BRAF mutation) and type 2-CRC (CIMP-high/MSI-low/MSS/BRAF mutation) [7, 35].

2.2.4 Hereditary Non-polyposis Colon Carcinogenesis

Hereditary non-polyposis colon cancer (HNPCC) shows a right-sided (~70 %) or even (30 % of cases) colonic distribution of cancer and mainly non-polypous precursor lesions (0–IIa and 0–IIb) with predominant villous architecture, containing high-grade dysplasia as well as mucinous differentiation [36–42]. On initial and follow-up surveillance colonoscopy, detection rate for non-polypoid adenomas is about 1.1 per patient [37, 39]. The progression to HGD is more common in proximal than in distal HNPCC adenomas [42]. A high proportion of these non-polypoid adenomas will rapidly progress to cancer – CIMP-negative and with microsatellite instability (MSI-high) or chromosomal instability (and MS-stable) [7, 43].

2.2.5 *Dysplasia-Associated Lesion or Mass (DALM)–Cancer Pathway in Ulcerative Colitis*

Patients with ulcerative colitis or colitis Crohn may exhibit three different types of neoplastic lesions: *sporadic adenoma* (*or adenoma-like DALM*), *non-adenoma-like DALM*, *and flat dysplasia* [44].

Sporadic adenomas are adenomas in the part of the colon not involved in ulcerative colitis (or colitis Crohn) and without dysplasia of the surrounding flat mucosa (which shows pit pattern I or II). Similar lesions are protruding "*adenoma-like DALMs*" in non-dysplastic mucosa with chronic ulcerative colitis [45]. Endoscopic ablation is indicated, but they carry a low risk (0–4.6 %) of associated dysplasia or cancer in the colon [46].

DALM are raised dysplastic lesions with concomitant dysplasia of the surrounding flat mucosa (showing pit pattern IIIL, IV, V) – also termed "*non-adenoma-like DALM*". This appears to be a "field cancerisation defect" on the basis of an inflammation–dysplasia–cancer sequence [24, 47] and has a high probability (38–84 %) of synchronous or metachronous cancer in chronic ulcerative colitis or colitis Crohn [24, 47]. Therefore, (sub)total colectomy is recommended for "non-adenoma-like DALM" in ulcerative colitis [44].

Flat dysplasias are similar to lesions type 0–IIb–c, sometimes even unrecognisable in chronic inflamed mucosa. In the case of high-grade dysplasia (HGD), cancer may already be present in 42–67 % of patients [44, 47]. Colectomy is recommended for flat HGD to prevent synchronous and metachronous cancer [44].

A prospective study on flat low-grade dysplasia (LGD) found only a 3 % initial rate and a 10 % rate of subsequent progression to CRC within 10 years [48]. However, a more recent meta-analysis (477 patients) indicated that flat low-grade dysplasia (LGD) had a risk of 22 % for synchronous cancer and a 5-year progression rate of 33–53 % to advanced neoplasia (CRC or HGD) [49].

2.3 Characteristics of Gastric Carcinomas

Gastric adenocarcinomas occur in approximately *90 %* of cases *sporadically* and in *10 %* as *inherited* – the latter comprise at least three forms: familial diffuse gastric cancer (*FDGC*), familial intestinal gastric cancer (*FIGC*), and hereditary diffuse gastric cancer (*HDGC*) which is caused by CDH1 germline mutations encoding the cell-adhesion protein E-cadherin [50]. The two main *histogenetic types* of gastric cancer are the *intestinal type* forming gland-like tubular structures (most with grading G1 or G2) and the *diffuse type* lacking cell cohesion and infiltrating the gastric wall by spreading of single cancer cells (grading G3) (Fig. 2.2) [8, 51, 52].

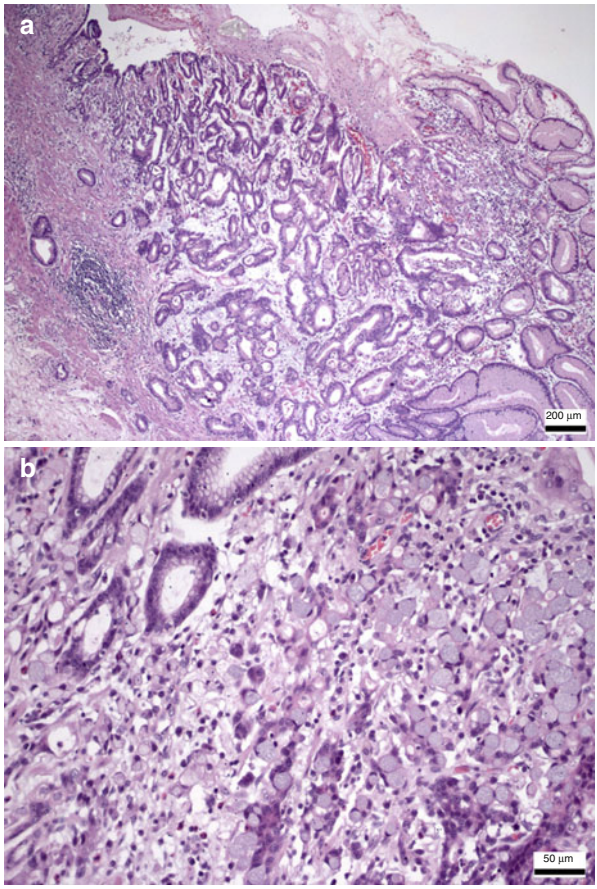

Fig. 2.2 Typical histomorphology of intestinal type (**a**) and diffuse/signet ring (**b**) gastric adenocarcinoma indicating the different growth pattern of well-defined glands in intestinal type in contrast to discohesive tumour sheet in diffuse type of gastric cancer

2.3.1 Intestinal-Type Gastric Adenocarcinoma

Intestinal-type cancer comprises two major histogenetic phenotypes – the intestinal phenotype and the gastric phenotype [9, 53]. The *classical intestinal phenotype* arises in chronic atrophic gastritis (either autoimmune type A or *Helicobacter pylori*-induced type B gastritis) via the "immature" intestinal metaplasia to flat or adenomatous intraepithelial neoplasia and finally the gland-forming intestinal-type carcinoma which frequently shows solid tumour growth and less invasion [9, 53, 54]. Intestinal metaplasia with HGIN has a 33–85 % chance to progress to gastric cancer [55]. Quite seldom are sporadic gastric adenomas that carry a 35 % chance of carcinomatous foci [55].

Early gastric cancers of the intestinal type may exhibit any of the macroscopic lesions (0–Ip/s, 0–IIa/b/c, 0–III). Polypoid adenomas play a minor role as precursor

lesion for gastric cancer, since <5 % of gastric cancers originate from 0–Is adenomas. The risk of submucosal invasion is high in types 0–Is and even higher in type 0–IIc [6]. The risk of lymph node metastasis is low (<5 %), when submucosal invasion is <500 μm (Ly 0, V 0), but is 21 % for invasion of sm2 >500 μm [2, 17].

2.3.2 *Gastric Phenotype Adenocarcinoma*

The gastric phenotype carcinoma – frequently with microsatellite instability – develops from non-metaplastic gastric epithelium either "de novo" or from small adenoma of pyloric mucoid glands [54, 56]. Gastric-type differentiated carcinoma represents 8–24 % of early gastric cancers, often type IIb or IIc lesions with indistinct margins and less discoloured surface [53]. This type of cancer tends to be larger and more often exhibits submucosal invasion than the intestinal type [9, 53, 54]. Advanced gastric-type and intestinal-type cancers often express a mixed phenotype including a diffuse growth component caused by inactivation of the E-cadherin gene CDH1, e.g. by biallelic hypermethylation [54].

2.3.3 *Diffuse/Signet Ring-Type GC (De Novo GC)*

Early diffuse-type cancer shows either flat (type 0–IIb) or depressed lesions (0–IIc), with diffusely infiltrating single cancer cells in the mucosa and submucosa which exhibit massive cellular atypia (most with grading G3) [6, 57]. Minute diffuse-type cancers (diameter <5 mm) are difficult to detect and most often appear as small or tiny pale spot in the gastric mucosa [57].

2.3.4 *Hereditary Diffuse-Type Gastric Cancer (HDGC)*

The origin of this cancer (caused by CDH1 germline mutations) in subjects <60 years old usually is multifocal synchronous, and neoplastic foci are very difficult to detect in affected individuals. Therefore, in suspected cases, the diagnosis must be established by molecular genetic analysis, starting with the index case in the kindred. Individuals with proven inherited genetic defect must undergo prophylactic gastrectomy [50].

2.4 Characteristics of Oesophageal Neoplastic Lesions

For both types of oesophageal cancer, squamous cell carcinoma as well as adenocarcinoma in columnar cell-lined (Barrett's) oesophagus (CLE) (Fig. 2.3), chronic inflammation of the oesophageal epithelium is the trigger of carcinogenesis.

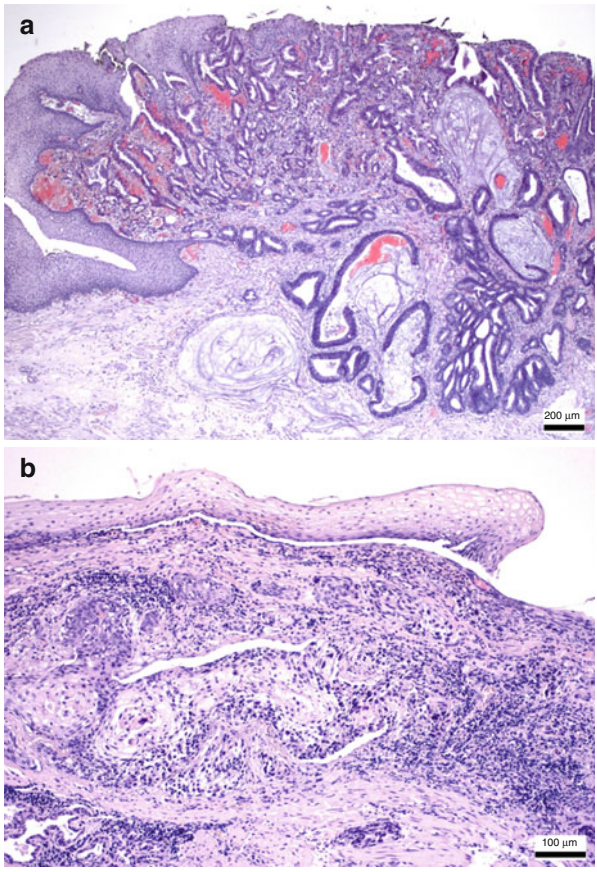

Fig. 2.3 Histomorphology of Barrett's cancer (**a**) and squamous epithelial cancer of the oesophagus (**b**) revealing atypical tubular glands of Barrett's oesophagus as well as irregular-formed squamous cell nests with keratin pearls with extension of the squamous epithelium above it in both cases

The chronic oesophagitis–dysplasia–cancer sequence is maintained by a host of noxious agents in the former and mainly by gastro-oesophageal reflux of acid and pepsin or bile in the latter [58].

2.4.1 Cylinder Epithelial Dysplasia–Cancer Pathway (Barrett's Cancer)

Chronic erosive reflux oesophagitis triggers mucosal healing by transition to more resistant columnar cell-lined metaplasia and finally dysplastic epithelium [59]. Additional risk factors are tobacco and alcohol abuse [58]. Nearly all adenocarcinomas of the distal oesophagus and the EG junction arise from Barrett's epithelium via the sequence "intestinal metaplasia–dysplasia–carcinoma in situ". In a high proportion of early neoplasias, the Wnt-β-catenin pathway is activated and p53 mutated [60]. Low-grade dysplasia may either regress again or progress to high-grade intraepithelial neoplasia (HGIN) which carries on the average a 30 % chance of

concurrent carcinomatous foci [60]. In Barrett's oesophagus, the harder-to-detect flat lesions (0–IIa–c) are by far the most frequent macroscopic types of neoplastic lesion [6] (compare Chap. 7).

2.4.2 Squamous Epithelial Cell Dysplasia–Cancer Pathway

Chronic oesophagitis may be caused by a variety of irritants of the squamous cell epithelium such as caustic damage (hot drinks/food), chronic alcohol use often combined with carcinogens from tobacco use or nutritional deficiencies (vitamins A, B1–B6, C; zinc), and also chronic viral infection (e.g. human papilloma virus) [55, 58]. Chronic inflammation combined with carcinogen exposure leads to squamous epithelial dysplasia. Epithelial dysplasias are classically divided into low, moderate, or severe grade, whereby a two-tier grading system of low grade and high grade was established due to poor interobserver agreement [10].

Early lesions appear as reddish spots or small grey–white or plaque-like elevations of the mucosa, apparent intraepithelial neoplasms (HGIN) or carcinoma in situ [3, 61]. About half of these lesions are located in the middle third and the remainder equally in the upper and lower thirds of the oesophagus – and about 10 % are synchronous multifocal [3, 6, 62]. Most of them are well- or moderately differentiated squamous cell carcinomas (grading G1 or G2), but due to the thin submucosal layer rich in lymphatic vessels, the risk of early local spread is high [3].

2.5 Processing of Mucosectomy Specimens

The resected specimen has to be sent to the pathology laboratory in distended and orientated fashion, mounted with pins (every 1.5 mm, 0.5 mm from the margin) onto a cork or rubber board, and immersed in 4 % buffered formaldehyde solution. It is recommended that specimens are cut into slices 2 mm thick for subserial microscopic examination [3].

The histology of the mucosectomy specimen (EMR en bloc or ESD) must evaluate:

- Macroscopic type 0 and subtypes
- Low- or high-grade intraepithelial neoplasia or carcinoma
- Completeness of resection at the margins of the specimen
- Any invasion of the submucosa as depth beyond the muscularis mucosae

The *pathology report* confirms the safety of a local excision or recommends additional surgical resection, based on:

- Qualitative criteria (grading, lymphatic or venous vascular invasion, tumour budding, cribriform pattern)
- Quantitative criteria (width and depth of invasion into the submucosa)

As mentioned, the depth of invasion correlates with risk of lymph node metastasis (Table 2.1) [1–3]. Quantitative micrometre (μm) measurement are reported from the lower limit of the muscularis mucosae, when the position of the muscularis mucosae can be determined precisely in the area of the tumour invasion. Rigorous analysis of the excised lesion provides a quality standard for therapeutic endoscopy and serves as a safeguard against erroneous decisions, such as unnecessary surgical resection of a non-neoplastic lesion or the inappropriate endoscopic resection (R1 or R2) of a carcinoma with submucosal invasion.

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