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REVIEW AND PERSPECTIVE

Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors

Günter Klöppel · Guido Rindi · Martin Anlauf · Aurel Perren · Paul Komminoth

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Abstract The gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are composed of cells with a neuroendocrine phenotype. Well-differentiated tumors, well-differentiated carcinomas, poorly differentiated carcinomas, functioning tumors (with a hormonal syndrome), and nonfunctioning tumors are identified. To predict their clinical behavior, these neuroendocrine tumors are classified on the basis of their clinicopathological features, including size, local invasion, angioinvasion, proliferative activity, histological differentiation, and metastases, into neoplasms with benign, uncertain, low-grade malignant and high-grade malignant behavior. In addition, a tumor/nodes/metastases classification and a grading system are presented. In the light of these criteria, the various GEP-NET entities are reviewed.

Keywords Neuroendocrine tumors · Gut · Pancreas · Pathology · Classification · Biology · Prognosis

G. Klöppel (✉) · M. Anlauf
Department of Pathology, University of Kiel,
Michaelisstr. 11,
24105 Kiel, Germany
e-mail: guenterkloeppel@path.uni-kiel.de

G. Rindi
Department of Pathology, University of Parma,
Parma, Italy

A. Perren
Department of Pathology, Technical University of Munich,
Munich, Germany

P. Komminoth
Institute of Pathology, Stadtspital Triemli,
Zurich, Switzerland

Introduction

The neuroendocrine tumors (NETs) of the gastrointestinal tract and the pancreas express antigens that are also common in nerve elements. These antigens have been referred to as neuroendocrine markers, and their demonstration in normal cells and neoplasms has led to the terms neuroendocrine cell system and neuroendocrine neoplasms. Markers of the neuroendocrine phenotype such as synaptophysin, chromogranins A, B, and C [89], HISL-19, neuron-specific enolase (NSE), the proprotein convertases PC2 and PC3, the lymphoreticular epitope Leu-7, and the neural cell adhesion molecule (or CD56) reveal the neuroendocrine differentiation of gastroenteropancreatic NETs (GEP-NETs), independent of hormone production [88].

This review discusses the various GEP-NET entities that are observed in the foregut, midgut, and hindgut regions. The GEP-NETs associated with hereditary diseases and the molecular changes in GEP-NETs are dealt with in separate papers in this issue [5, 117].

Classification

In the gastrointestinal tract and pancreas, 15 neuroendocrine cell types producing different hormones but all expressing the general neuroendocrine marker synaptophysin can be distinguished [150]. They are the source of GEP-NETs. Traditionally, they are separated into benign or malignant neoplasms. In this paper, however, we follow the concept that all GEP-NETs are potentially malignant but differ in their metastasizing capacity (i.e., their biological behavior), depending on a number of features and criteria (see below).

The functional diversity of the neuroendocrine cell types and their nonrandom distribution in the gut and pancreas are probably the reason for the complexity of the tumors derived from them. Classifying these tumors is therefore extremely difficult. In 1963, Williams and Sandler [173] classified the GEP-NETs into foregut (stomach, duodenum, upper jejunum, and pancreas), midgut (lower jejunum, ileum, appendix, and cecum), and hindgut (colon and rectum) tumors, with considerable clinicopathological differences between the three groups. However, in the case of the foregut tumors, the usefulness of such a classification in practical diagnostic work is limited by its failure to characterize individual tumor entities with well-defined histological, hormonal, and/or clinicopathological profiles. The World Health Organization (WHO) 2000 classification, based on earlier work [28], therefore follows a different approach. In a first step, it distinguishes between pure endocrine tumors and mixed endocrine–exocrine tumors (for mixed tumors, see article by Volante et al. (in this issue and [167]). In a second step, a uniform scheme of classification is applied to all pure GEP-NETs, identifying three tumor categories, irrespective of their site of origin:

(1) Well-differentiated endocrine tumors with benign (a) or uncertain behavior (b) at the time of diagnosis
(2) Well-differentiated endocrine tumors with low grade malignant behavior
(3) Poorly differentiated endocrine carcinomas with high-grade malignant behavior

In a third step, the well-differentiated, slowly growing NETs and carcinomas of the gastrointestinal tract and the pancreas, those that are also called carcinoids [110] and islet cell tumors, respectively, and which comprise a number of well defined entities (e.g., insulinomas, gastrinomas, and others), are distinguished on the basis of their localization as well as their morphological and functional features. Poorly differentiated NETs that are composed of cells displaying high mitotic activity and few secretory granules form a separate group, as they are not difficult to recognize as invariably high-grade malignancies.

Undisputable criteria that predict the biological behavior of well-differentiated GEP-NETs are gross tumor infiltration of adjacent organs and/or metastases. Adverse prognostic factors include tumor size, angioinvasion, mitotic activity, and an elevated Ki-67/MiB-1 proliferative index (higher than 2%) [29, 58]. Tables 1 and 2, based on the WHO criteria, provide checklists that allow an appropriate classification of an individual GEP-NET.

As there is an increased demand for a standard in the stratification and treatment of patients with GEP-NETs, the European Neuroendocrine Tumour Society recently developed guidelines that were supplemented by a proposal for tumor/nodes/metastases (TNM) classification [127, 128]. Apart from theTNM staging proposal, a working formulation for the grading of GEP-NETs based on mitotic count and Ki-67 index has been suggested. Both the staging proposal and the grading system still need to be validated.

Epidemiology

Incidence data on GEP-NETs are difficult to obtain because of the rarity of these neoplasms, their long clinical courses, their incomplete recognition, and their classification, which was for a long time rather inaccurate. The Surveillance, Epidemiology, and End Results (SEER) data on carcinoids, which are usually cited when the incidence of GEP-NETs are discussed [99], are probably inexact for gastric and duodenal NETs, as the general availability of endoscopy

Table 1 Criteria for assessing the prognosis of neuroendocrine tumors of the gastrointestinal tract

Biological behavior	Metastases	Invasion of muscularis propria[a]	Histological differentiation	Tumor size (cm)	Angioinvasion	Ki-67 index (%)	Hormonal syndrome
Benign	−	−	Well differentiated	≤1[a]	−	<2	−[a]
Benign or low-grade malignant	−	−	Well differentiated	≤2	−/+	<2	−
Low-grade malignant	+	+[b]	Well differentiated	>2	+	>2	+
High-grade malignant	+	+	Poorly differentiated	Any	+	>20	−

[a] Exception: malignant duodenal gastrinomas are usually smaller than 1 cm and confined to the submucosa
[b] Exception: benign NETs of the appendix usually invade the muscularis propria

Table 2 Criteria for assessing the prognosis of neuroendocrine tumors of the pancreas

Biological behavior	Metastases	Invasion[a]	Histological differentiation	Tumor size (cm)	Angioinvasion	Ki-67 index (%)	Hormonal syndrome
Benign	–	–	Well differentiated	≤1	–	<2	–/+[b]
Benign or low-grade malignant	–	–	Well differentiated	>2	–/+	<2	–/+[c]
Low-grade malignant	+	+	Well differentiated	>3	+	>2	+[c]
High-grade malignant	+	+	Poorly differentiated	Any	+	>20	–

[a] Invasion of adjacent organs (e.g., duodenum, stomach)
[b] Insulinomas
[c] Insulinomas and other functioning tumours (e.g., glucagonomas)

has led to a considerable increase in the rates of these NETs that is not yet reflected in the SEER data. For these reasons, the following incidence figures for the NETs of the gut are interpreted with caution. The incidence of all NETs of the gut has been estimated according to a recent Swedish study to be 2.0/100,000 for men and 2.4/100,000 for women [59].

NETs of the esophagus are very rare and represent only 0.05% of all gastrointestinal NETs or approximately 1% of all esophageal cancers [34, 100]. Most patients are men, who are mainly in the sixth to seventh decade [87].

NETs of the stomach were thought to account for 2–4% of all gastrointestinal NETs [99, 100]. However, as the incidence of gastric NETs has not yet really been determined after the increased application of endoscopy, it is quite possible that gastric NETs may lead the list of the most frequent gastrointestinal NETs and account for 11–41% [75]. In Japan, they represent 30% of all gastrointestinal carcinoids.

Duodenal NETs account for approximately 2% of all gastrointestinal NETs in the old series [53, 100]. In more recent series, however, duodenal and jejunal NETs amounted to 22% of all gastrointestinal NETs [33]. The tumors occur slightly more frequently in men (male/female ratio=1.5:1) and are usually seen in the fifth and sixth decade [33].

Ileal NETs account for approximately 25% of all gastrointestinal NETs [33]. Men and women are affected equally. Their age ranges from the third to the tenth decade but has a peak in the sixth decade.

Appendiceal NETs account for approximately 20% of all NETs in the gastrointestinal tract [92, 100]. They are the most frequent tumors in the appendix. In contrast to all other NETs of the gastrointestinal tract, they most commonly present in the second to third decade and affect women more frequently than men [95, 110]. They may also occur in children [9].

While colon NETs are rare, NETs of the rectum account for 20% of the gastrointestinal NETs [32]. Their sex distribution is equal. An increase in incidence in colonic and rectal NETs has been observed in recent years [59, 85, 92, 99, 146]. In western countries, NETs of the colon are primarily diagnosed in male patients during the seventh decade of life and rectal lesions in the sixth decade [59]. A similar trend is observed in women, although at a relatively younger age, in the fifth decade in the colon and the sixth in the rectum [59]. Poorly differentiated neuroendocrine carcinomas develop predominantly in male patients [20].

The prevalence rate of PETs has been estimated at less than 1 in 100,000 [101]. Their incidence is not known, but it is probably substantially lower because of the generally rather favorable prognosis of PETs. For insulinomas alone, an incidence of approximately four tumors per 1 million patient-years has been calculated [141]. PETs appear at any age but occur preferentially between 30 and 60 years. There is no significant gender selection but a slight female preponderance of 55% to 45%.

PETs account for 1–2% of all pancreatic neoplasms [151]. Syndromic or functioning PETs (i.e., PETs that cause hormonal syndromes) make up 60%, with insulinomas being the most frequent type (up to 70%), followed by gastrinomas [22, 73, 76, 79, 135].

Insulinomas have been diagnosed in all age groups. The highest incidence is found between 40 and 60 years. Women seem to be slightly more frequently affected than men (ratio 6:4) [49, 51, 52, 84, 140, 141, 165].

Gastrinomas account for about 20% of endocrine pancreatic tumors [56, 151]. Zollinger–Ellison syndrome (ZES) is more common in men than in women, with a ratio of 3:2, and the mean age at diagnosis is 38 years [13, 27, 69, 126, 154].

Glucagonomas represent about 5% of all clinically relevant pancreatic endocrine tumors and 8% of functioning tumors [151]. The patients most often present between the ages of 40 and 70 years and women are slightly more often affected [136].

VIPomas constitute 3–8% of all pancreatic endocrine tumors, and women are more often (70%) affected than men.

Nonfunctioning PETs may occur at any age; however, they are rare in childhood [143]. Clinically relevant

nonfunctioning PETs are rare, with a prevalence of 0.2–2 per million inhabitants [58]. Small nonfunctioning PETs including microadenomas are much more frequent, with a reported prevalence in autopsy studies from 0.4 to 1.5% (largely depending upon the amount of pancreatic tissue examined) [54, 74]. There is no gender predilection [62].

Esophagus

Most NETs of the esophagus are poorly differentiated neuroendocrine carcinomas and mixed endocrine–exocrine carcinomas, usually of large size (from 4 to 10 cm in diameter) and located in the lower third of the esophagus [34]. They present as fungating or ulcerated masses deeply infiltrating into the esophageal wall and are associated with early spread to the regional lymph nodes or infiltration of adjacent organs. In contrast, most well-differentiated NETs/neuroendocrine carcinomas are less than 4 cm in diameter and present as polypoid lesions. Only few of them were found to be associated with lymph node metastases [61, 115].

Poorly differentiated neuroendocrine carcinomas of the esophagus are often of the large cell type and only positive for synaptophysin (Fig. 1). Well-differentiated NETs/carcinomas show a solid or trabecular–glandular growth pattern and are strongly immunoreactive for synaptophysin and chromogranin A, but mostly negative for the hormones expressed in the gastrointestinal tract. No established grading and staging scheme exists for these NETs.

The majority of well-differentiated esophageal NETs/carcinomas were found in association with Barrett's esophagus and adenocarcinomas. We saw two well-differentiated NETs of the esophagus. Both were incidental findings and associated with heterotopic oxyntic mucosa. They stained strongly positive for the vesicular monoamine transporter 2 (VMAT2) suggesting an origin from the enterochromaffin-like (ECL) cells within heterotopic oxyntic mucosa.

The initial symptoms of these tumors are unspecific because they are functionally silent. Inappropriate antidiuretic hormone syndrome, hypercalcemia, or ectopic production of vasoactive intestinal polypeptide (VIP) have been reported in only single poorly differentiated neuroendocrine carcinomas [34, 66, 169]. Well-differentiated NETs of the esophagus are rarely associated with lymph node metastases and thus have an excellent prognosis. Eleven patients suffering from primary esophageal well-differentiated NETs/neuroendocrine carcinomas for which follow-up was available were all alive and disease-free at 1–23 years after surgical excision (mean 5.5 years). The overall survival of patients with poorly differentiated carcinomas is usually less than 6 months [68, 83]. Mixed endocrine–exocrine carcinomas of the esophagus show a prognosis similar to that of adenocarcinomas, depending on their histological differentiation and tumor stage [36]. Neither associated diseases nor inherited syndromes have been reported for NETs/neuroendocrine carcinomas of the esophagus.

Stomach

There are three distinct types of NETs in the stomach [129], and if the poorly differentiated NET is added, four types of NETs can be distinguished [35, 75]. Type 1 comprises approximately 70–80% of all cases, followed by types 3, 2, and 4 [129]. Recently, a proposal for a TNM staging classification and a grading system for tumors of the stomach was published (Tables 3, 4, and 5).

Type 1 NETs of the stomach present as multiple small tumors (0.3–1 cm; Fig. 2a). Histologically, they are well differentiated (proliferation rate <2%), show a solid pattern, and are composed of intensely synaptophysin and

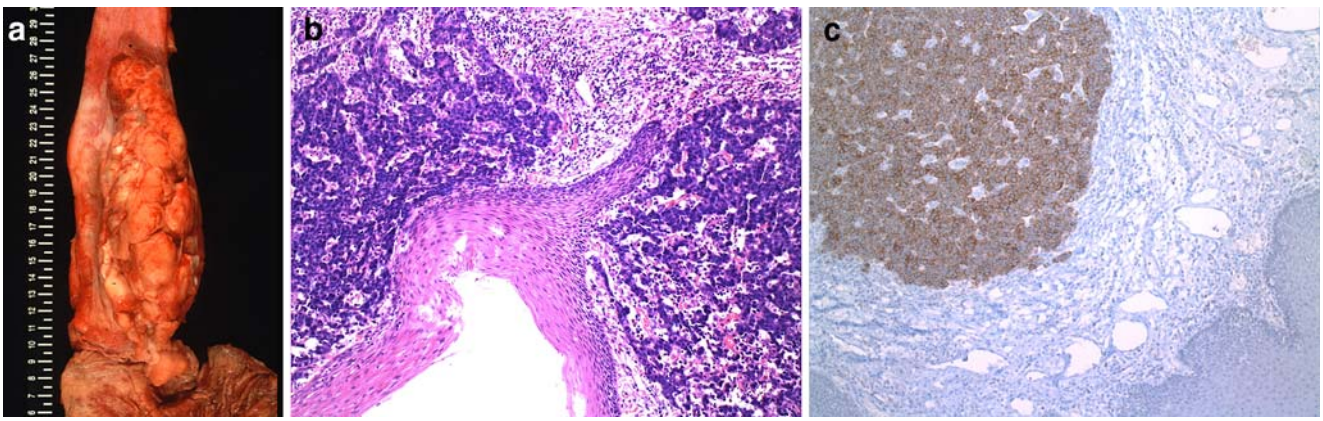

Fig. 1 Poorly differentiated neuroendocrine carcinoma of the esophagus (**a**) with subepithelial infiltration by large atypical (**b**) and synaptophysin-positive cells (**c**)

Table 3 Proposal for a pTNM classification for neuroendocrine tumors of the stomach [127]

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	In situ tumor/dysplasia (<0.5 cm)
T1	Tumor invades lamina propria or submucosa and ≤1 cm
T2	Tumor invades muscularis propria or subserosa or >1 cm
T3	Tumor penetrates serosa
T4	Tumor invades adjacent structures
	For any T add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

chromogranin A positive ECL cells. These cells, which produce histamin, are specifically recognized by the marker VMAT2 [45, 130] (Fig. 2b). In addition to the tumors, there is always ECL cell hyperplasia in the oxyntic mucosa. The tumors are not associated with any hormonal syndrome but are always found on a background of chronic atrophic gastritis of the oxyntic mucosa of the autoimmune type. This disease occurs mainly in women, aged between 50 and 60 (70–80% of the patients) and leads to the disappearance of the specific glands of the oxyntic mucosa harboring the parietal cells. The consequences of the loss of parietal cells are the insufficient production of intrinsic factor, which triggers pernicious anemia via the decreased resorption of vitamin B12, and deficient production of gastric acid, which stimulates the antral G cells to persistent hypersecretion of gastrin. It is thought that hypergastrinemia promotes the growth of the ECL cells of the oxyntic mucosa so that diffusion to micronodular ECL cell hyperplasia develops and, after a latent period of many years, multiple ECL tumors [14]. The observation that the tumors can also occur in only partially atrophic gastritis and the detection of growth factors such as tumor growth

Table 4 Proposal for disease staging for neuroendocrine tumors of the stomach

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	any N	M1

Table 5 Proposal for a grading system for neuroendocrine tumors [127]

Grade	Mitotic count (10HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a] Ten HPF: high power field=2 mm^2, at least 40 fields evaluated in areas at highest mitotic density
[b] MiB1 antibody
Percent of 2,000 cells in areas of highest nuclear labeling

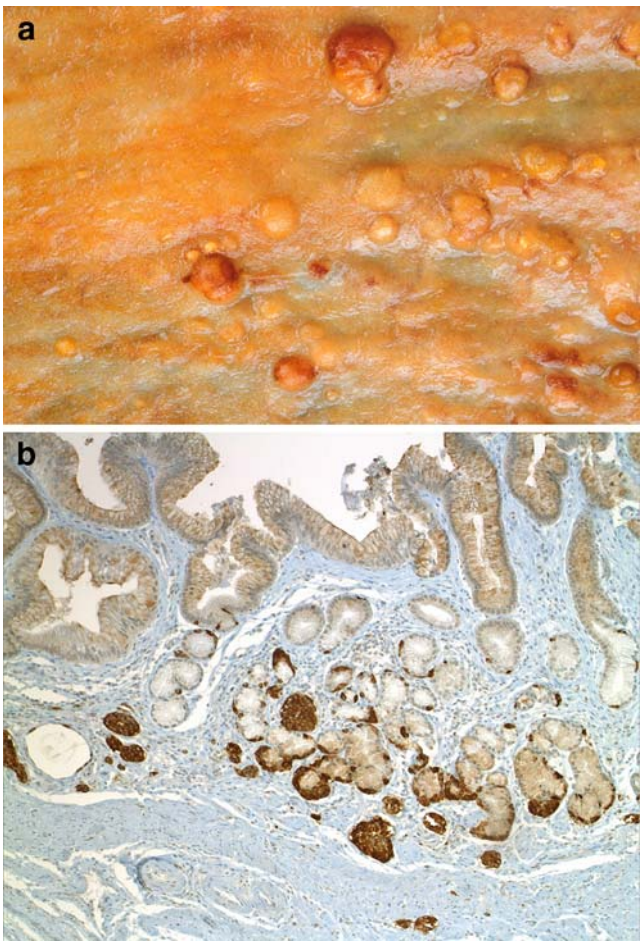

Fig. 2 Well-differentiated neuroendocrine tumors of the stomach associated with chronic atrophic gastritis of the oxyntic mucosa (type 1 gastric NET): **a** multiple small polypoid tumors in the corpus region of the stomach. **b** VMAT2-positive ECL cell hyperplasia in the oxyntic mucosa with microtumors

factor alpha, basic fibroblast growth factor, and B cell leukemia/lymphoma 2 are indications that hypergastrinemia alone probably does not cause these tumors to develop [14, 17]. The prognosis of these tumors is good because they are usually so small that they can be removed endoscopically. Regional lymph node metastases seem to occur only in those very rare cases in which the tumors are larger than 2 cm in size and infiltrate the muscularis propria [124].

Type 2 gastric NETs occur in association with multiple endocrine neoplasia type 1 (MEN1), a hereditary, autosomal dominant disorder, in the course of which a ZES has developed. The genetic changes associated with MEN1 are probably needed for tumor development [42] because so far no such tumors have been found in patients with ZES but without MEN1. As in type 1 NETs, multiple ECL cell NETs are found in the oxyntic mucosa, which, however, is not atrophic but hypertrophic. Men and women with a mean age of 50 years are equally affected [35]. Lymph node metastases may develop in rare cases in which the tumors exceed a size of 1–2 cm [149].

Type 3 gastric NETs are sporadic (unassociated with MEN1) solitary tumors that develop unrelated to chronic atrophic gastritis and occur throughout the stomach (Fig. 3). In one third of the cases, the tumor is already larger than 2 cm at the time of diagnosis. Histologically, they are well differentiated, show a trabecular to solid pattern, and often have a proliferation rate exceeding 2–5%. They consist in most cases of ECL cells. Tumors with EC (serotonin) cells or gastrin cells, by contrast, are extremely rare [75]. They show a predilection for the male sex and occur at a mean age of 55 years [35]. If the tumor is larger than 2 cm, has invaded the muscular layer, and/or shows angioinvasion, metastases are very likely to be present [35]. In 71% of such cases that were surgically removed, lymph node metastases were found [35]. In rare cases, type 3 tumors may be associated with a so-called atypical carcinoid syndrome, characterized by cutaneous flushing in the absence of diarrhea, usually coupled with liver metastases and production of histamine and 5-hydroxytryptophan [35].

Poorly differentiated neuroendocrine carcinomas of the stomach ("type 4 gastric NETs") are rare. Histologically, they often show no special arrangement of the cells, which are medium sized, with a chromatin-rich nucleus and sparse cytoplasm. Immunohistochemically, they are positive for synaptophysin and to some extent also for chromogranin A. Hormones cannot be demonstrated. These tumors are more common in men than in women, aged between 60 to 70 years. They present as a large ulcerated lump with symptoms similar to those of adenocarcinomas, including gastric hemorrhage and obstruction. Hormonal symptoms are absent, and there is no relationship to chronic atrophic gastritis but, in exceptional cases, to MEN1 [16]. At the time of diagnosis, most of the tumors are already in an advanced stage (tumor diameter more than 4 cm) and show extensive metastasis. Their prognosis is poor, with three quarters of the patients dying within 1 year of diagnosis because of extensive metastatic disease [16]. In addition, poorly differentiated large cell neuroendocrine carcinomas or mixed endocrine–exocrine carcinomas (endocrine differentiation in greater than 30% of the tumor) may occur but are extremely rare. Mixed exocrine–endocrine carcinomas should generally be classified as adenocarcinomas [35].

Recently, multiple, up to 1.3 cm large ECL cell tumors were found in a background of ECL cell hyperplasia and parietal cell hyperplasia in patients with hypergastrinemia but without ZES [1, 112]. It was suggested that the development of these NETs is associated with an intrinsic acid secretion abnormality of the parietal cells.

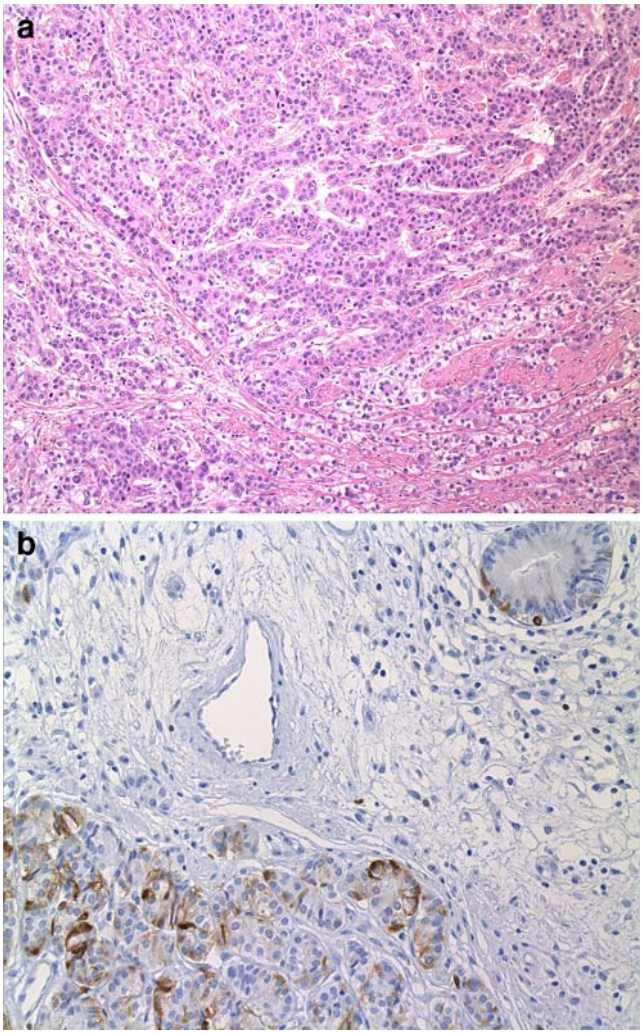

Fig. 3 Well-differentiated neuroendocrine carcinoma of the stomach (**a**) unrelated to chronic atrophic gastritis (type 3 gastric NET). VMAT2-positive ECL cell tumor (**b**)

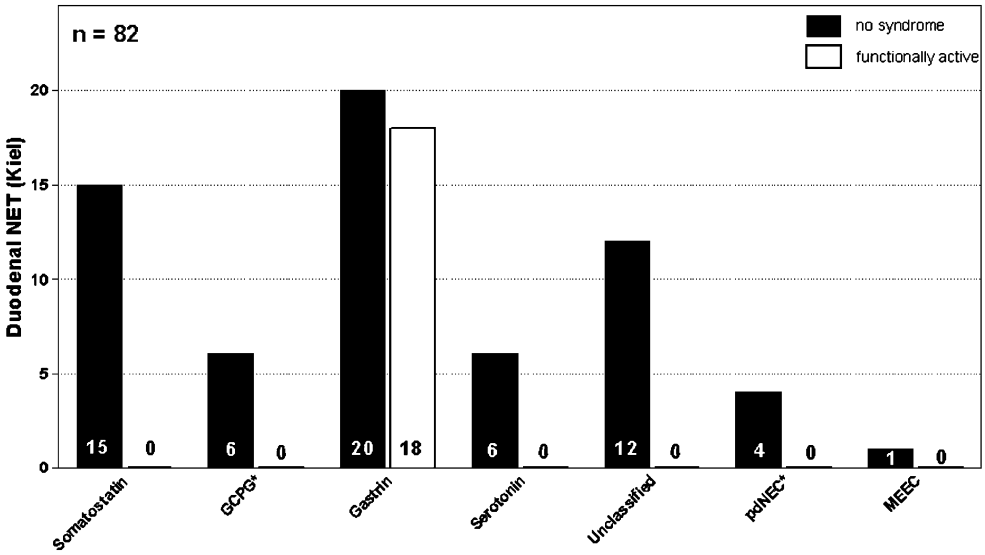

Fig. 4 Relative ratios of neuroendocrine tumors of the duodenum defined by their hormone expression. Neuroendocrine tumor archives of the Department of Pathology, University of Kiel, 1970 and 2006

Duodenum and upper jejunum

On the basis of their clinical, morphological, hormonal, and genetic features, several types have to be distinguished: gastrin-producing NETs with ZES (i.e., gastrinomas), gastrin-producing NETs without ZES, somatostatin-producing tumors with or without neurofibromatosis type 1 (NF1), serotonin- or calcitonin-producing NETs, poorly differentiated neuroendocrine carcinomas, and gangliocytic paragangliomas [14, 25, 28, 152]. Their relative frequency is shown in Fig. 4. Tables 6 and 7 show the recently proposed TNM classification for these NETs.

Gastrin-producing and gastrin-secreting NETs causing a ZES are called gastrinomas. Twenty-five to 33% occur in the setting of an MEN1 syndrome. Sporadic and MEN1-associated duodenal gastrinomas usually arise in the first part of the duodenum [43, 109, 156, 163]. They usually form small (<2 cm in diameter) polypoid lesions within the submucosa with an intact or focally ulcerated overlying mucosa (Fig. 5). In a large series of 96 duodenal NETs, the mean size was 0.8 cm for gastrinomas [31, 156]. The gastrinomas in MEN1 are multiple and tiny (sometimes less than 1 mm in diameter) [7]. Both the sporadic and MEN1 gastrinomas are well differentiated, showing a trabecular–pseudoglandular pattern. They all stain for gastrin. Caudal-related homeobox 2 (CDX2) is positive in half of the cases. MEN1-associated gastrinomas are associated with focally accentuated gastrin and somatostatin cell hyperplasia in the mucosa and/or Brunner's glands, while sporadic gastrinomas lack such lesions [6, 7]. Despite their small size, metastases to regional lymph nodes are already found in 60 to 80% of the cases at the time of diagnosis [162, 170]. These metastases may be much larger than the primary tumor and may erroneously be considered pancreatic tumors, especially if they are located at the upper margin of the head of the pancreas [43]. This peculiarity is probably the reason why in early reports primary lymph node gastrinomas were diagnosed and many more pancreatic gastrinomas were recorded than today. Apart from lymph node metastases, duodenal gastrinomas may metas-

Table 6 Proposal for a pTNM classification for neuroendocrine tumors of the duodenum/ampulla/proximal jejunum

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumors
T1	Tumor invades lamina propria oder submucosa and size ≤1 cm
T2	Tumor invades muscularis propria or >1 cm
T3	Tumor invades pancreas or retroperitoneum
T4	Tumor invades peritoneum oder other organs
	For any T: add (m) for multiple tumors
N—regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
M—distant metastases	
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Table 7 Proposal for disease staging for neuroendocrine tumors of the duodenum/ampulla/proximal jejunum

Stage	T	N	M
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

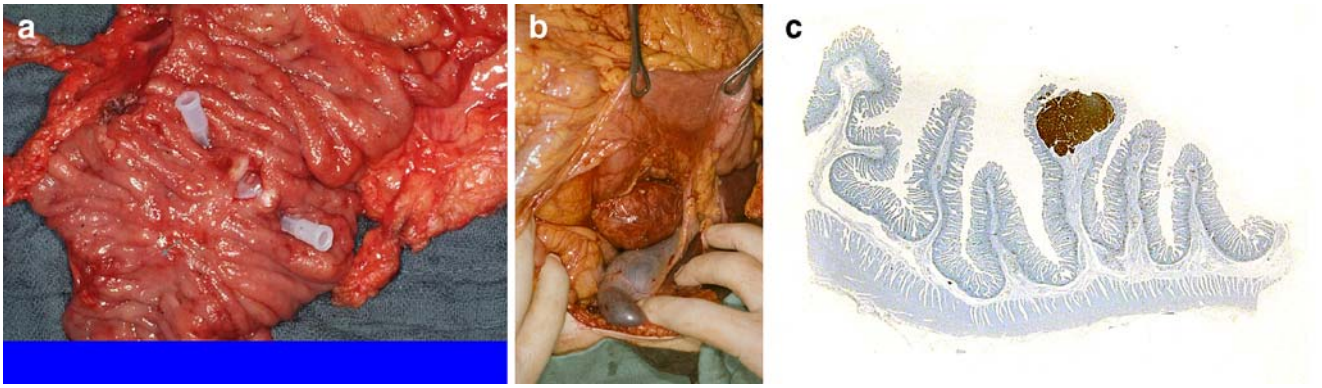

Fig. 5 Well-differentiated neuroendocrine carcinoma of the duodenum producing gastrin and associated with a Zollinger–Ellison syndrome. **a** Duodenal mucosa showing a small submucosal tumor. **b** Lymph node metastasis at the upper margin of the pancreas. **c** Duodenal mucosa with a gastrin-positive NET

tasize to the liver but only in a small percentage of cases (approximately 10%) and only many years after the manifestation of the disease. Thus, 10-year survival rates of 84% have been reported in patients with duodenal gastrinomas [107, 162, 170]. Fast-growing poorly differentiated and metastasizing duodenal gastrinomas are extremely rare.

The ZES is characterized by elevated fasting gastrin serum levels, a positive gastrin secretin stimulation test, and clinical symptoms such as recurrent peptic ulcer disease, gastroesophageal reflux disease, and occasional diarrhea [8, 176]. Between 60 and 75% of patients with sporadic ZES are found to have a duodenal gastrinoma, while the remaining patients are found to have a pancreatic gastrinoma. In MEN1-associated ZES, most, if not all, patients have their gastrinomas in the duodenum [4, 8, 118, 119].

Somatostatin-producing tumors account for approximately 20% of all duodenal NETs (Table 2). Their preferential localization is in the region of the papilla of Vater, and their mean size is 2.3 cm [31, 41, 156]. Histologically, these tumors often have a glandular pattern, frequently with psammoma bodies in the lumina. About 50% of the somatostatin-producing tumors lack chromogranin A immunoreactivity but stain brightly for synaptophysin and somatostatin. If the tumors invade the muscularis propria, metastasis to the paraduodenal lymph nodes has probably occurred [41]. They are not associated with a hormonal syndrome, particularly not with a somatostatinoma syndrome, but may be found in association with NF1 [33, 156]. There are no morphological features to distinguish between NF1- and non-NF1-associated duodenal NETs.

Gangliocytic paragangliomas are rare (Table 2). They are mainly found in the second (periampullary) portion of the duodenum, and their size ranges from 1.5 to 7 cm [31, 125, 156]. The tumors are composed of three different mature cell types: (1) epithelial/endocrine cells, which are arranged in ribbons, solid nests, or pseudoglandular structures, (2) S100-positive neural spindle cells, which usually represent the major component, and (3) scattered or aggregated ganglionic cells. Despite their infiltrative growth, metastasis to the regional lymph nodes is rarely observed [24, 67, 137].

Well-differentiated duodenal NETs producing gastrin but not associated with a ZES have been increasingly recog-

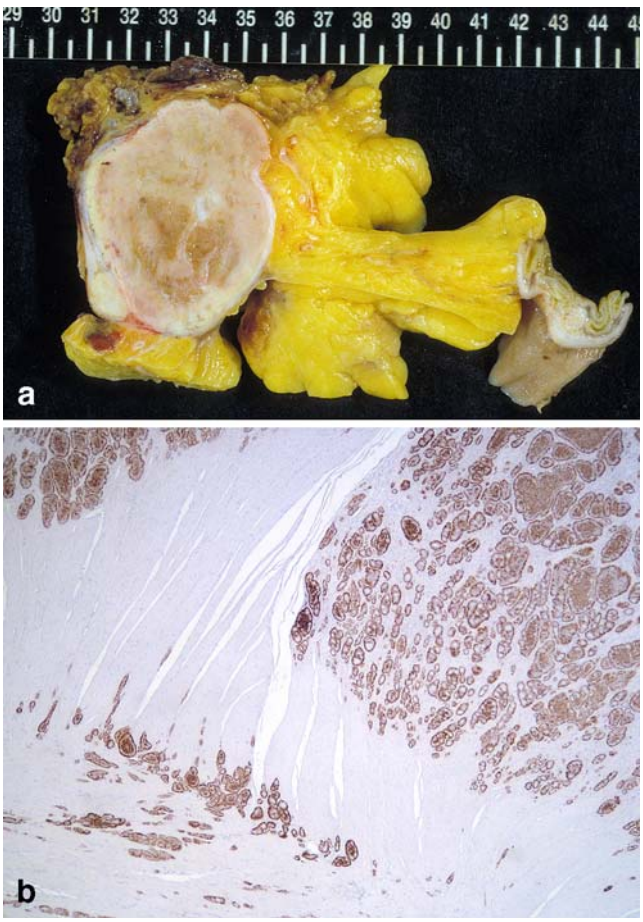

Fig. 6 Small neuroendocrine carcinoma of the ileum with large lymph node metastasis in the mesenterium (**a**). The tumor infiltrates the muscular layer and produces serotonin (**b**)

nized during recent years and are so far not well characterized. They are mostly found in the duodenal bulb as small polypous tumors localized in the mucosa and submucosa. Histologically and immunohistochemically, they are indistinguishable from gastrinomas. Recently, a series of these NETs were reported in patients who were on proton pump blockers and had *Helicobacter pylori* [97]. These tumors were found to be associated with gastrin cell hyperplasia in the adjacent mucosa. Clinically, they are often incidental findings during endoscopy or cause symptoms by virtue of local infiltration such as obstructive jaundice, pancreatitis, hemorrhage, and intestinal obstruction [33]. The prognosis of this group of nonfunctioning tumors is much more favorable than ZES-associated gastrinomas or ampullary somatostatinomas [33]. Metastases are not to be expected until the tumor extends beyond the submucosa.

In rare cases, there are well-differentiated duodenal NETs producing serotonin or calcitonin [31, 156]. Their biology is not well characterized but seems to follow the criteria listed in Tables 6 and 7.

Poorly differentiated neuroendocrine carcinomas of the duodenum occur primarily in the region of the papilla of Vater. They present as ulcerated or protuberant tumors ranging in size between 2 and 3 cm [33]. Histologically, they show a solid arrangement of medium-sized or large cells staining for synaptophysin but only rarely for chromogranin A. A small number of tumor cells may also stain for somatostatin. Clinically, most patients develop jaundice and/or hemorrhage. Hormonally, they are inactive. At the time of diagnosis, advanced metastasis to the regional lymph nodes and the liver has usually occurred [104].

Table 8 Proposal for a TNM classification for neuroendocrine tumors of the lower jejunum and ileum

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa and size ≤1 cm
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades subserosa
T4	Tumor invades peritoneum/other organs
	For any T add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Neuroendocrine tumors of the distal jejunum, ileum, and Meckel's diverticulum

The well-differentiated NETs (carcinoids) of the lower jejunum and the ileum present as small sessile nodules with a diameter ranging between 0.5 and 3 cm but usually between 1 and 2 cm. Most of them occur in the terminal ileum, close to the ileocecal valve, and in 26–30% of the cases, they are multiple [26, 116, 175]. Tumors that are larger than 1 cm almost invariably show infiltration of the muscular layer and the adjacent subserosal fatty tissue. On the cut surface, they are yellow and small (Fig. 6a). Histologically, they are characterized by an insular growth pattern with solid to cribriform tumor structures showing pallisading of the peripheral cell layer. In the glandular cavities, there are sometimes PAS-positive material. The tumor structures are embedded in a sclerotic paucicellular stroma that may lead to kinking of the foregut and subsequently to bowel obstruction. The uniform tumor cells have faintly eosinophilic cytoplasm and a very low mitotic rate, and immunohistochemically, they show the phenotype of serotonin-producing enterochromaffin (EC) cells (Fig. 6b). Between the tumor cells, there may be single S100-positive cells [26]. In addition, carcinoembryonic antigen is found in approximately two thirds of the tumors. The tumor cells may also express neurotransmitters and are positive for CDX2 [81]. There is no endocrine cell hyperplasia in the mucosa adjacent to or distant from the tumors.

If the tumors are smaller than 1 cm in diameter, lymph node metastases are rare, not exceeding 5% of the cases. If the tumors are larger than 2 cm, lymph node metastases are present in 85% of the cases, and very often, there are also liver metastases [158]. The lymph node metastases lie in the mesenterial tissue and are often larger than the primary.

Table 9 Proposal for disease staging for neuroendocrine tumors of the lower jejunum and ileum

Stage	T	N	M
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	any T	N1	M0
Stage IV	any T	any N	M1

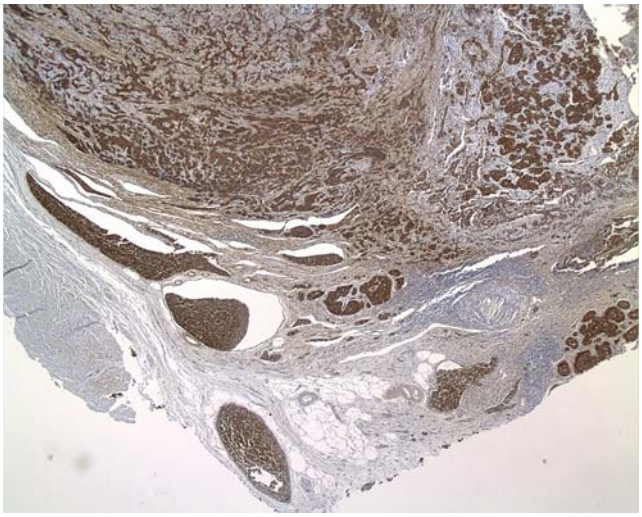

Fig. 7 Well-differentiated serotonin-producing neuroendocrine carcinoma of the appendix with infiltration of the mesoappendixand angioinvasion

Tables 8 and 9 show the newly developed TNM staging system for the tumors [128].

Clinically, the tumors may be discovered during exploration of the gut in search of a primary tumor that gave rise to liver metastases, or the patients have local (bowel obstruction, subileus) and/or systemic symptoms. The systemic symptoms are due to the hormonal effects of serotonin and are called carcinoid syndrome. This is characterized by flush, diarrhea, and carcinoid heart disease mostly causing right-sided heart failure because of tricuspid regurgitation. The carcinoid syndrome is usually seen in patients with liver metastases (95%). However, in some cases, liver metastases can occur without the syndrome. Carcinoid heart disease is a rather late event in the carcinoid syndrome and is responsible for a large number of deaths in these patients. Overall 5-year survival rates range from 50 to 60%, decreasing to 35% if liver metastases are present [158]. There is no association with any known hereditary disease, but approximately one third of the patients have other, mostly intestinal, carcinomas, either synchronous or metachronous [26, 175].

Meckel's diverticulum is a rare site of well-differentiated NETs. These tumors are usually small (<1.7 cm) and when found incidentally have not yet metastasized [26]. However, if symptomatic, metastases are likely to be found [98].

Table 10 Proposal for a TNM classification for neuroendocrine tumors of the appendix

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤1 cm invading submucosa and muscularis propria
T2	Tumor ≤ 2 cm invading submucosa, muscularis propria and/or minimally (up to 3 mm) subserosa/mesoappendix
T3	Tumor >2 cm and/or extensive (more than 3 mm) invasion of subserosa/mesoappendix
T4	Tumor invades peritoneum/other organs
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Neuroendocrine tumors of the appendix

The well-differentiated NETs/neuroendocrine carcinomas of the appendix (appendiceal carcinoids) usually occur in the tip of the organ, are 1–2 cm in size, and infiltrate the appendix wall. Histologically, they are characterized by a solid islet-like pattern (i.e., type A pattern according to Soga and Tazawa [147]. Rarely, they show trabeculae and ribbons (Soga's type B). Tumor cells are uniform, with low atypia and rare mitoses, if any. The tumors with a solid pattern are composed of serotonin-producing EC cells. In addition, there are sustentacular cells that are positive for S-100 [150].

A size greater than 1 cm, a location at the base of the appendix, extensive involvement of the mesoappendix, and angioinvasion are important negative prognostic factors (Fig. 7) and are potentially associated with metastases [95]. The risk of lymph node metastases in tumors measuring 1 to 2 cm is 1% and increases to 30% in tumors measuring more than 2 cm [158]. Mesoappendix invasion is a debated variable [91, 134]. Series with sufficiently long follow-up, including children with a median age of 12 years, revealed that no patient treated by appendectomy died of appendiceal NETs with a diameter below 2 cm [114, 158]. A poorly differentiated neuroendocrine carcinoma, as part of a mixed

Table 11 Proposal for disease staging for neuroendocrine tumors of the appendix

Stage	T	N	M
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	any T	N1	M0
Stage IV	any T	any N	M1

exocrine–endocrine carcinoma, has only been reported once so far [133]. Tables 10 and 11 show the newly developed TNM stage system and the grading of the tumors [128].

Most tumors are usually detected because of symptoms of acute appendicitis. A carcinoid syndrome has not been reported in association with a metastasized well-differentiated appendiceal NET. The carcinoid syndrome is exceedingly rare [102].

Neuroendocrine tumors of the colon and rectum

Well-differentiated NETs (carcinoids) are more frequent in the rectum than the colon, whereas poorly differentiated neuroendocrine carcinomas are more common in the colon. The well-differentiated rectal tumors mostly appear during endoscopy as small (<1 cm) movable submucosal tumors. The poorly differentiated neuroendocrine carcinomas of the colon are usually of large size (>2 cm). An average diameter of 4.9 cm was reported [10], and 55 of 129 cases reported by Soga were between 5 and 10 cm in size [145]. The well-differentiated NETs of the colon are mostly small and occur in the cecal region [10, 132, 145] or throughout the colon in cases of ulcerative colitis [94]. Recently, "microcarcinoids" (0.5 to 1.5 mm in size) have been described in polypous colonic adenomas [122].

Histologically, the well-differentiated NETs (carcinoids) of the rectum are characterized by a trabecular pattern (Soga's type B) [150]. The well-differentiated NETs of the colon, in contrast, show the solid pattern that is also found in the tumors of the small intestine (Soga's type A) or a mixed pattern (Soga's type E) [145, 150]. Immunohistochemically, the well-differentiated NETs of the rectum are positive for synaptophysin, glucagon, glicentin, and/or pancreatic polypeptide and are usually negative for chromogranin. In addition to synaptophysin and chromogranin A, the well-differentiated NETs of the cecal region stain for serotonin. In minor tumor cell populations, positivity for motilin, neurotensin, substance P, enkephalins, and other hormones has been described [150]. In addition, prostatic acidic phosphatase was reported positive in the majority of the well-differentiated colorectal NETs, making this a potentially useful marker of lower hindgut origin [46]. Expression of the transcription factor CDX2, although specific for colorectal adenocarcinomas [123], proved to be restricted to the rare colorectal serotonin-positive NETs [81].

Histologically, poorly differentiated neuroendocrine carcinomas are characterized by solid structures, sometimes with "organoid" appearance, extensive "geographical chart" necrosis, small or large cell cytology and high mitotic counts, and Ki67 index [23, 38, 152]. Mucin stain (periodic acid Schiff [PAS] and Alcian/PAS) may be useful to identify occasional, although not uncommon, minor foci of adenocarcinoma or squamous cell carcinoma [20, 21]. Immunocytochemically, there is diffuse immunostaining for synaptophysin and CD56 as well as NSE, while chromogranin A may be absent or only present in individual cells. c-kit expression is found in approximately 20% of the cases and is not associated with an activating mutation in exon 11 of the c-kit gene [3].

Prognostically, well-differentiated NETs of the rectum but also of the colon are likely to have metastasized to the regional lymph nodes and elsewhere if they are larger than 2 cm and have invaded the muscularis propria. Rectal well differentiated NETs less than 1 cm in size have a very low risk of metastasis, while those between 1 and 2 cm may show metastasis to the regional lymph nodes in up to 5% of the cases. If the tumors are poorly differentiated, there is a high rate of metastasis at the time of diagnosis [20, 21]. A recent proposal for a TNM classification and grading system may be of value in the stratification and management of patients with colon and rectal NETs (Tables 12 and 13) [128]. NETs of the colon and rectum rarely cause hormonal symptoms. Some cases of classical carcinoid syndrome were reported in patients with metastatic lesions of cecal origin [144, 145, 150]. An association with inflammatory bowel diseases has been reported in both Crohn's and ulcerative colitis, suggesting that chronic inflammation is a potentially triggering condition for the development of NETs [63, 103, 150]. Synchronous or metachronous colorectal carcinomas are frequently seen [144, 145]. This is particularly the case in poorly differentiated neuroendo-

Table 12 Proposal for a TNM classification for neuroendocrine tumors of the colon and rectum

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa
	T1a size <1 cm
	T1b size 1–2 cm
T2	Tumor invades muscularis propria or size >2 cm
T3	Tumor invades subserosa/pericolic/perirectal fatty tissue
T4	Tumor directly invades other organs/structures and/or perforates visceral peritoneum
	For any T add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph node status cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M—distant metastases (subspecification as in small bowel)	
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Table 13 Proposal for disease staging for neuroendocrine tumors of the colon and rectum

Stage	T	N	M
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	any T	N1	M0
Stage IV	any T	any N	M1

crine carcinomas [21, 23, 47]. Therefore, a common histogenesis for neuroendocrine and nonneuroendocrine aggressive cancers of the colon has been discussed [164, 168].

Neuroendocrine tumors of the presacral region

NETs involving the presacral region between the rectum and the sacrum are rare but well documented [64, 161]. They affect adults of both sexes and are frequently associated with tail gut cysts. Histologically, most of them are well-differentiated NETs resembling rectal carcinoids. Metastases may occur.

Pancreas

Pancreatic NETs (PETs) usually present as solitary well-demarcated neoplasms but lack a well defined capsule (Fig. 8). Their size ranges between 1 and 5 cm. Multiple tumors are rare and should always raise the suspicion of MEN1 or VHL (for details on hereditary NETs, see Anlauf et al. this issue). The majority of the tumors are well differentiated, showing a trabecular or solid pattern [77]. Poorly differentiated carcinomas, which are rare, show a diffuse infiltrative growth pattern.

The biological behavior, i.e., the metastatic potential, may be predicted by a number of criteria and indicators that are summarized in Table 2. Recent studies provided evidence that this multiparameter approach that is applied in the 2004 WHO classification of PETs is a reliable tool for stratifying patients into risk groups and that, in addition, the immunohistochemical marker CK19 may refine the prognostic power of the WHO classification [29, 58, 139]. Furthermore, a proposal for a TNM classification and a grading system has recently been published (Tables 14 and 15) [127].

PETs include several entities that are divided on the basis of their symptomatology into functioning neoplasms (i.e., with hormonal syndromes such as insulinomas, gastrinomas, glucagonomas, or VIPomas) and nonfunctioning neoplasms (i.e., without hormonal syndromes). The majority of the functioning and nonfunctioning PETs fall into the category of well-differentiated carcinomas, with the exception of insulinomas.

Insulinoma These tumors are located in the pancreas or are directly attached to it and present as solitary red brown, mostly soft, well-demarcated tumors with a size between 0.5 and 2 cm. Histologically, they show either solid or trabecular, gland-like tumor growth [56, 79]. The tumor cells are often bland, and cells with large, pleomorphic nuclei are rare. If they occur, they are not predictive of malignancy. A special finding in insulinomas is the deposition of amyloid that can be immunostained for amylin [172]. Immunohistochemically, they stain for insulin and proinsulin. In addition there may be cells

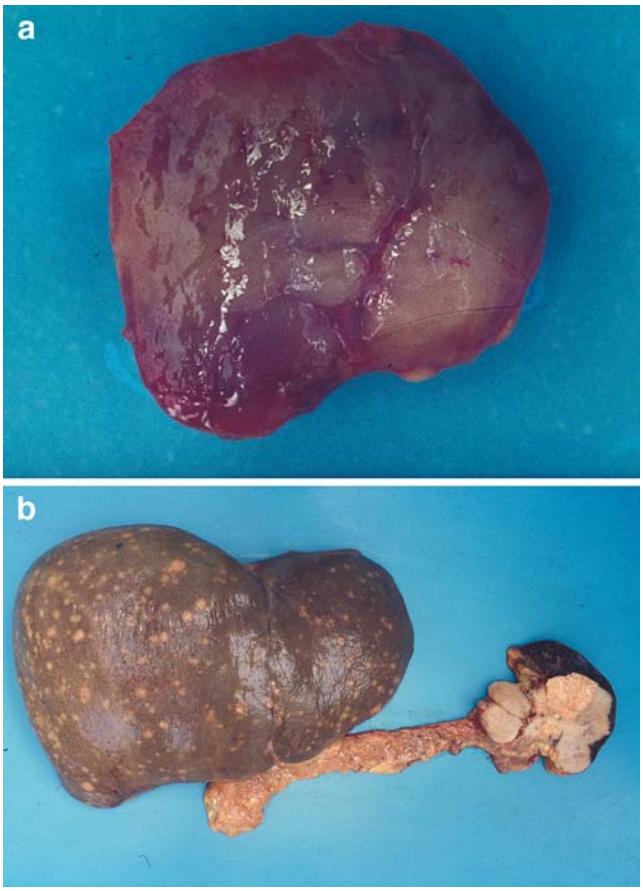

Fig. 8 Pancreatic neuroendocrine tumors: **a** tumor with a diameter less than 2 cm (insulinoma without metastases). **b** Large tumor (>2 cm) in the tail of the pancreas with multiple liver metastases (malignant insulinoma)

Table 14 Proposal for a pTNM classification and disease staging for endocrine tumors of the pancreas

Abbreviation	Characteristics
T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Limited to the pancreas and size <2 cm
T2	Limited to the pancreas and size 2–4 cm
T3	Limited to the pancreas and size >4 cm or invading duodenum or bile duct
T4	Invading the wall of adjacent large vessels (celiac axis or superior mesenteric artery), stomach, spleen, colon, adrenal gland
	For any T add (m) for multiple tumors
N—regional lymph nodes	
NX	Regional lymph node status not assessed
N0	Absence of lymph node metastasis
N1	Presence of regional lymph node metastasis
M—distant metastases	
MX	Distant metastasis not assessed
M0	Absence of distant metastases
M1	Distant metastasis

expressing glucagon, somatostatin, pancreatic polypeptide or other hormones [72, 79].

The vast majority of insulinomas are benign at the time of diagnosis [151]. This may be due in part to their early detection, as they already become symptomatic at a small size [78, 148] (Fig. 8a). Approximately 8.4% of insulinomas are malignant [49, 51, 52, 84, 140, 148, 157, 165] (Fig. 8b). Malignant insulinomas occur in an older age group and are rare in children [39, 159].

Tumors producing a hypoglycemic syndrome are usually larger than 1 cm; microadenomas (below 0.5 cm in diameter) are functionally silent. Approximately 4–7% of patients with insulinomas suffer from MEN1 [141]. Rare examples of insulinomas have also been described in patients suffering from NF1 [48]. Between 12 and 17% of VHL patients develop endocrine pancreatic tumors, which may show focal insulin immunoreactivity [90], but most of these tumors are clinically nonfunctioning.

Gastrinoma In recent years, it has become obvious that pancreatic gastrinomas are less common than duodenal gastrinomas (see "Duodenum and upper jejenum"). They are associated with the sporadic form of ZES and only very rarely with the MEN1-associated form of ZES [118, 119]. Their preferential localization seems to be in the pancreatic head, where they present as solitary tumors that usually have a diameter of 2 cm or more [43, 153]. The anatomical area comprising the head of the pancreas, the superior and ascending portion of the duodenum, and the relevant lymph nodes has been called the "gastrinoma triangle," as it harbors the vast majority of these tumors [65, 70, 105, 106, 153]. Histologically, they predominantly show a mixed trabecular and solid pattern with some pseudoglandular structures. Immunohistochemically, they are positive for gastrin but may also show some glucagon, somatostatin, or pancreatic polypeptide cells [15, 119]. The risk of liver metastases increases with tumor size, and they occur with a frequency of 30% [151]. Metastases to other organs are rare [155]. In general, the progression of gastrinomas is relatively slow with a combined 5-year survival rate of 65% amd a 10-year survival rate of 51% [70]. Even with metastatic disease, a 10-year survival of 46% (lymph node metastases) and 40% (liver metastases) has been reported [108]. Patients with complete tumor resection have 5- and 10-year survival rates of 90–100%, respectively.

Glucagonoma These are NETs that produce glucagon and are associated a syndrome consisting of skin rash (necrolytic migratory erythema), mild glucose intolerance, anemia, weight loss, depression, diarrhea, and a tendency to develop deep-vein thrombosis [58]. They are usually large, solitary tumors with a diameter between 3 and 7 cm commonly occurring in the tail of the pancreas [136, 151]. Extrapancreatic glucagonomas are extremely rare [131]. On their cut surface, they show a brown red to pink color and a soft consistency. Histologically, they display a mixed trabecular and solid pattern, and immunohistochemically, they stain (often weakly) for glucagon or proglucagon-derived peptides (glicentin, glucagon-like peptides 1 and 2) [18, 55, 136]. In addition, numerous pancreatic polypeptide cells can often be identified.

Approximately 60–70% of glucagonomas are already metastatic at the time of diagnosis [60, 121, 136]. Malignant glucagonomas tend to grow slowly, and patients may survive for many years.

Table 15 Proposal for a pTNM classification and disease staging for endocrine tumors of the pancreas

Stage	T	N	M
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	any T	N1	M0
Stage IV	any T	any N	M1

VIPoma This PET is associated with the Verner–Morrison syndrome or WDHA syndrome (watery diarrhea, hypokalemia, hypochlorhydria, alkalosis), characterized by diarrhea (up to 20 l a day), hypokalemia because of potassium loss in the stool, achlorhydria, glucose intolerance, and anemia. These symptoms are caused by inappropriate secretion of VIP and peptide histidine methionine (PHM). The tumors are located in the pancreas, where they are preferentially seen in the tail. They are large and solitary [30]. Histologically, they show a solid or trabecular growth pattern. Immunohistochemically, they stain for VIP and PHM and often in addition for pancreatic polypeptide and other hormones [2, 12, 111].

Most VIPomas have led to metastases in the regional lymph nodes and the liver at the time of diagnosis [93]. The 5-year survival rate is about 59% for patients with metastases and 94% for those without metastases [58].

Somatostatin-producing PETs (so-called somatostatinomas) In 1979, the somatostatinoma syndrome was described in patients presenting with symptoms of diabetes mellitus, cholecystolithiasis, steatorrhea, indigestion, hypochlorhydria, and occasionally anemia in association with a somatostatin-producing and somatostatin-secreting PET [80, 82, 120, 142, 166]. The symptoms were attributed to the inhibitory effects of somatostatin on the function of various cell systems. However, since then, no further convincing reports on the somatostatinoma syndrome have appeared in the literature, although somatostatin-producing NETs (SOM-NETs) have been identified not only in the pancreas but also at other sites, particularly the duodenum [41, 160]. This casts doubt on the existence of a somatostatinoma syndrome and raises the question whether the described symptoms were unspecific manifestations of large malignant PETs [166] that happened to produce somatostatin. The last view is supported by our results in a series of 386 PETs, collected between 1972 and 2006, which contains ten well-differentiated somatostatin-producing PETs, none of which were associated with the so-called somatostatinoma syndrome [50].

SOM-NETs of the pancreas are rare and in approximately 50% of the cases malignant. While most tumors show a trabecular pattern, some display a paraganglioma-like architecture with occasional psammomatous calcifications. The somatostatin-producing PETs in our series were outnumbered by the SOM-NETs found in the duodenum (see "Duodenum and upper jejenum") [31, 156].

Other functioning PETs Apart from insulinomas, gastrinomas, glucagonomas, and VIPomas there may be adrenocorticotropic hormone-producing tumors causing Cushings's syndrome [37, 57, 96], tumors producing growth hormone-releasing hormone (GHRH) causing acromegaly [11, 19, 40, 138], calcitonin-producing tumors causing diarrhea [44, 71], and serotonin-producing tumors causing a carcinoid syndrome [113, 171]. Many of these neoplasms are solitary and large and have metastasized to the liver and lymph nodes when detected. Histologically, they do not differ from the more common functioning tumors. Exceptions are some GHRH-producing tumors, which show a distinct paraganglion-like microglandular pattern and spindle-shaped cells [138]. The hormone causing the syndrome can usually be detected by immunohistochemistry. These tumors tend to be large, and at diagnosis, many patients have already liver metastases. The prognosis is therefore usually poor [58].

Nonfunctioning PETs These PETs are either incidental findings or become clinically apparent because of size, invasion of adjacent organs, or the occurrence of metastases. In rare cases, they present as pancreatitis. They are observed more frequently than previously, although this probably does not reflect an actual increase in frequency but rather improved diagnostic methods [139]. Historically, most of these tumors were large when detected and frequently malignant [73]. More recently, however, smaller nonfunctioning tumors are increasingly detected by modern imaging techniques [139]. Large nonfunctioning PETs are reported to occur most frequently in the head of the pancreas, possibly because they are most likely to produce symptoms such as cholestasis in this location. In general, the presenting symptoms are most often unspecific and may consist of nausea, vomiting, or diarrhea.

Histologically, they may show various types of patterns: a trabecular, solid, pseudoglandular, or gyriform pattern. Immunohistochemically, these tumors stain for synaptophysin and chromogranin A and show a wide range of positivity for hormones including glucagon, somatostatin, and pancreatic polypeptide. Some of these tumors are associated with elevated hormone levels in the blood (e.g., glucagon, somatostatin, or pancreatic polypeptide), reflecting the hormonal immunoreactivity in the tumor. Because the patients lack any hormonal syndrome, they should not be called glucagonomas, somatostatinomas, or Ppomas. A special feature of glucagon-producing but hormonally silent NETs are grossly cystic changes [86, 174].

A minority of nonfunctioning NETs of the pancreas are histologically poorly differentiated, showing a diffuse infiltrative growth pattern and composed of small- to medium-sized cells, occasionally also large cells, that have a high mitotic rate and proliferative activity of more than 20%. Their neuroendocrine differentiation is demonstrated by diffuse staining for synaptophysin and, rarely, for

chromogranin A. Hormones are usually not detected.They may stain for p53.

Prognostically, well-differentiated nonfunctioning NETs of the pancreas have a 5-year survival rate of approximately 65% and a 10-year survival rate of 45%. Follow-up in patients with PETs having a diameter of less than 2 cm revealed that they are often cured by surgery [139].

Tumors smaller than 0.5 cm are designated microadenomas and are usually not visible macroscopically. Most of these tumors are detected incidentally or at autopsy and are present throughout the pancreas. Histologically, they show a trabecular pattern, and immunohistochemically, they stain for glucagon.

Conflicts of interest statement We declare that we have no conflict of interest.

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