

# Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms

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## Abstract

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are composed of cells with a neuroendocrine phenotype. The old and the new WHO classifications distinguish between well-differentiated and poorly differentiated neoplasms. All well-differentiated neoplasms, regardless of whether they behave benignly or develop metastases, will be called neuroendocrine tumours (NETs), and graded G1 (Ki67 <2%) or G2 (Ki67 2–20%). All poorly differentiated neoplasms will be termed neuroendocrine carcinomas (NECs) and graded G3 (Ki67 >20%). To stratify the GEP-NETs and GEP-NECs regarding their prognosis, they are now further classified according to TNM-stage systems that were recently proposed by the European Neuroendocrine Tumour Society (ENETS) and the AJCC/UICC. In the light of these criteria the pathology and biology of the various NETs and NECs of the gastrointestinal tract (including the oesophagus) and the pancreas are reviewed.

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## Introduction

Endocrine neoplasms can be divided according to the chemical nature of their secretion products into two groups. Neoplasms that produce and secrete (glyco)-peptide hormones and biogenic amines comprise the first group. The second group includes the tumours that generate steroid hormones. The tumours of the first group are called neuroendocrine neoplasms (NENs) because of the marker proteins that they share with the neural cell system. These markers are synaptophysin and neuron-specific enolase. Other markers that also recognise the neuroendocrine phenotype are the chromogranins A, B and C and the proprotein convertases PC2 and PC3 (Lloyd 2003, Klöppel *et al.* 2007). The neural cell adhesion molecule CD56 is positive in many NENs, but is not specific for these tumours (Klöppel *et al.* 2009).

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Under the electron microscope the NENs show typical neurosecretory granules.

This review deals with the classification of the gastroenteropancreatic NENs (GEP-NENs) and discusses briefly the pathology and biology of the various GEP-NEN entities that are observed in the foregut, midgut and hindgut regions.

## Classification

The NENs arise from the neuroendocrine cell system that forms organoid cell aggregations or consists of disseminated cells in various organs of the body. In the gastrointestinal tract and pancreas, there are 15 different cell types defined by the hormonal products (Rindi & Klöppel 2004). Only eight of the 15 hormones that were identified in the cells of the gastrointestinal tract have so far been recognised in GEP-NENs. Many of these hormones give rise to hormonal syndromes, if they are produced and secreted by the majority of the tumour cells. The GEP-NENs that are associated with hormonal syndromes are then called insulinomas, glucagonomas, gastrinomas and serotoninomas. In addition, there are GEP-NENs that

produce hormones that are ectopic to the GEP system such as vasoactive intestinal polypeptide (VIP), ACTH or GH-releasing factor. GEP-NENs that are non-functioning (i.e. not associated with a hormonal syndrome), but immunohistochemically are found to be composed predominantly of – for instance – glucagon-expressing cells, may be called glucagon-producing NENs.

It seems that all GEP-NENs are potentially malignant neoplasms. However, the various entities that are recognised in the gastrointestinal tract and the pancreas differ considerably in their metastasising capacity (i.e. their behaviour). In addition, they differ in their hormonal cell composition and consequently in the associated hormonal syndromes. The reason for this biological complexity of the GEP-NENs is probably the functional diversity and nonrandom distribution of the various neuroendocrine cell types in the gut and pancreas, from which the tumours derive. It has therefore always been difficult to classify the GEP-NENs. Williams & Sandler (1963) classified the GEP-NENs by embryological origin as foregut (stomach, duodenum, upper jejunum and pancreas), midgut (lower jejunum, ileum, appendix and caecum) and hindgut (colon and rectum) tumours and found considerable clinicopathological differences among the three groups. However, with the recognition of many new GEP-NEN entities in the last two decades, especially among the foregut tumours, the usefulness of this classification in practical diagnostic work is more and more limited.

The WHO classification that appeared in 2000 for the NENs of the gastrointestinal tract (Solcia *et al.* 2000), and in 2004 for the NENs of the pancreas (Heitz *et al.* 2004), followed a new approach that attempted to predict the biological behaviour of GEP-NENs (Capella *et al.* 1995). As a first step, it distinguished between pure endocrine tumours and mixed endocrine–exocrine tumours. In a second step, a uniform scheme of classification was applied to all pure GEP-NENs,

identifying three tumour categories, irrespective of their site of origin (see Table 1): 1) well-differentiated endocrine tumours (WDET) with probably benign behaviour, 2) WDET with uncertain behaviour and well-differentiated endocrine carcinomas with low-grade malignant behaviour and 3) poorly differentiated endocrine carcinomas with high-grade malignant behaviour.

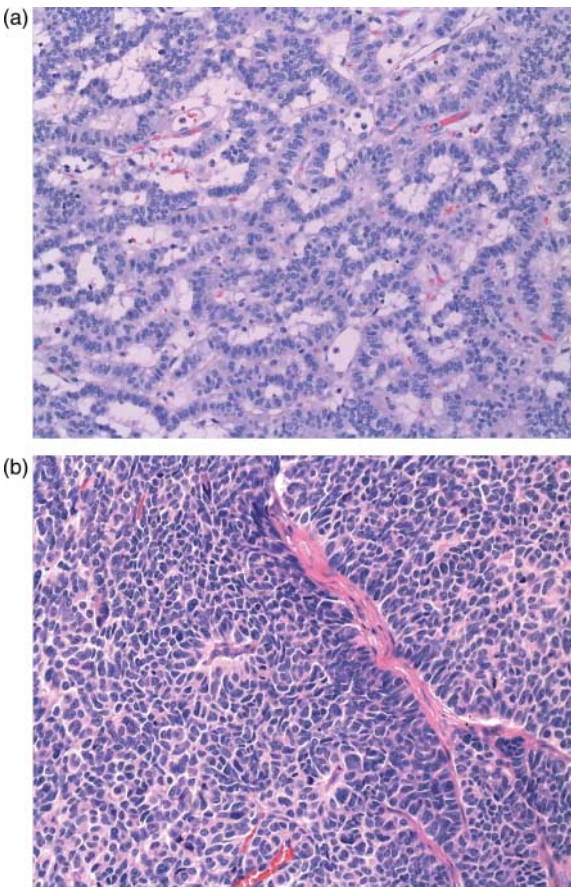
In a third step, the well-differentiated, low-grade-proliferative GEP-NENs (Fig. 1a) which are also called carcinoids in the gastrointestinal tract (Oberndorfer 1907) or islet cell tumours in the pancreas, were distinguished on the basis of their site of origin (stomach, duodenum, jejunum, ileum, appendix, colon and rectum and pancreas), size, gross and/or microscopic tumour extension, angioinvasion, proliferative activity (Ki67 index) and their syndromatic features (Solcia *et al.* 2000, Heitz *et al.* 2004). They were characterised by their immunostaining for synaptophysin and usually also for chromogranin A. Poorly differentiated NECs that were composed of highly proliferative cells formed a separate group because of their invariable high-grade malignancy (Fig. 1b). They were characterised by their diffuse immunostaining for synaptophysin, and only infrequent and sparse immunostaining for chromogranin A (Klöppel *et al.* 2009).

In recent years, it was felt that the WHO classification should be supplemented by criteria that may refine the prognostic stratification of GEP-NENs to allow a better stage-adjusted treatment of the patients. Therefore, the European Neuroendocrine Tumour Society (ENETS) developed guidelines for the diagnosis and treatment of GEP-NENs that contained site-specific TNM-classifications (Rindi *et al.* 2006, 2007). In addition, a three-tiered grading system of GEP-NENs based on mitotic count and Ki67 index (Rindi *et al.* 2006, 2007) and a standardised diagnostic procedure were suggested (Klöppel *et al.* 2009). Both grade 1 (Ki67 index <2%) and grade 2 (Ki67

**Table 1** Comparison of the 2010 WHO classification for gastroenteropancreatic neuroendocrine neoplasms with previous WHO classifications

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumour (WDET) <sup>a</sup> 2. Well-differentiated endocrine carcinoma (WDEC) <sup>a</sup> 3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC) 4. Mixed exocrine–endocrine carcinoma (MEEC)	1. Neuroendocrine tumour (NET) G1 (carcinoid) G2 <sup>a</sup> 2. Neuroendocrine carcinoma (NEC) G3 large cell or small cell type 3. Mixed adenoneuroendocrine carcinoma (MANEC)
II. Pseudotumour lesions	5. Tumour-like lesions (TLL)	4. Hyperplastic and preneoplastic lesions

G, grade (for definition, see text).  
<sup>a</sup>In case that the Ki67 proliferation rate exceeds 20%, this NET may be graded G3.



**Figure 1** (a) Well-differentiated neuroendocrine tumour. (b) Poorly differentiated neuroendocrine carcinoma.

index 2–20%) NENs are considered well-differentiated tumours, whereas grade 3 (Ki67 index > 20%) characterises the poorly differentiated tumours. Both the staging proposal and the grading system were recently validated for foregut and particularly pancreatic NENs (PanNENs) by several studies and their biological relevance and power to discriminate among prognostic groups was largely confirmed (Ekeblad *et al.* 2008, Fischer *et al.* 2008, Pape *et al.* 2008, La Rosa *et al.* 2009, Scarpa *et al.* 2010).

Unfortunately, the recently published seventh edition of the AJCC/UICC (Sobin *et al.* 2009) contains a TNM classification of well-differentiated neuroendocrine tumours (NETs; carcinoids) of the gastrointestinal tract and the pancreas that differs in a number of criteria from the ENETS-TNM system (Klöppel *et al.* 2010). It does not apply to high-grade (large and small cells) neuroendocrine carcinomas (NECs) and does not exactly follow the ENETS classifications for some of the anatomic sites (see Table 2 for the pancreas). No data are presented to justify the use of different

staging parameters. The result is that there now exist two parallel systems, each of which uses identical TNM terminology but may refer to different types and extents of disease for certain GEP-NENs. This discrepancy will lead to much confusion among clinicians and will likely limit the ability to compare research (Klöppel *et al.* 2010).

In the second half of 2010, a revised version of the WHO classification of GEP-NENs appeared (Rindi *et al.* 2010). This new classification introduced several changes. First, the label ‘neuroendocrine’ was now officially adopted to indicate neoplastic cells expressing neural markers such as synaptophysin. Secondly, the term ‘NEN’ encompasses all well and poorly differentiated tumours of the neuroendocrine cells. Thirdly, the pure NENs of the gastrointestinal tract and pancreas are stratified into two groups (Table 1): 1) the well-differentiated NETs and 2) the poorly differentiated NECs. The NETs are then separated by their proliferative activity into either G1 (equivalent to carcinoids) or G2 NETs. The NECs, that are G3 tumours, are subtyped into small cell and large cell neoplasms (see Table 1). TNM-staging of tumour extension according to tumour site leads to a further stratification of NETs and NECs. The neoplasms that show in addition to neuroendocrine cells (exceeding at least 30% of all tumour cells) non-endocrine components (usually adenocarcinoma structures) are distinguished from the pure NENs and called mixed adenoneuroendocrine carcinomas (Table 1).

## Pathology

### Origin, distribution and relative frequency

The cells that give rise to GEP-NENs derive from gastrointestinal stem cells that are able to differentiate into neuroendocrine cells. It is likely that the well and the poorly differentiated NENs come from different types of tumour stem cells. Analysing the development

**Table 2** Comparison of the criteria for the T category in the ENETS and UICC TNM classifications of pancreatic neuroendocrine tumours

	ENETS TNM	UICC TNM
T1	Confined to pancreas, < 2 cm	Confined to pancreas, < 2 cm
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, 2–4 cm
T3	Confined to pancreas, > 4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without vascular invasion
T4	Peripancreatic spread with invasion of large vessels or adjacent organs	Vascular invasion (truncus coeliacus, superior mesenteric artery)



of NENs of the pancreas and duodenum in multiple endocrine neoplasia type 1 (MEN1) it was found that a hyperplastic preprogrammed (i.e. hormonally differentiated) neuroendocrine cell that carries the germ line mutation of the *MEN1* gene gives rise to well-differentiated low-grade malignant neoplasms by allelic loss of the 11q13 region of the chromosome 11 (Anlauf *et al.* 2007a,b, Perren *et al.* 2007). In contrast, in poorly differentiated NENs, which are on the other end of the differentiation spectrum of NENs, the cell of origin is most likely close to the intestinal stem cell. If this cell is tackled by mutational hits, multiple profound genetic alterations are initiated, such as p53 mutations, that lead to the development of high-grade malignant, poorly differentiated NENs.

GEP-NENs can occur anywhere in the GEP neuroendocrine cell system. However, they are not equally distributed, but concentrate at certain sites such as the gastric fundus–corpus, the proximal duodenum, the papilla of Vater, the terminal ileum, the tip of the appendix, the lower rectum and the pancreas. In the past NENs of the ileum and appendix were the most common GEP-NENs. Recent studies, however, revealed that probably the gastric NENs outnumber all other GEP-NENs (Klöppel *et al.* 2007, Niederle *et al.* 2010).

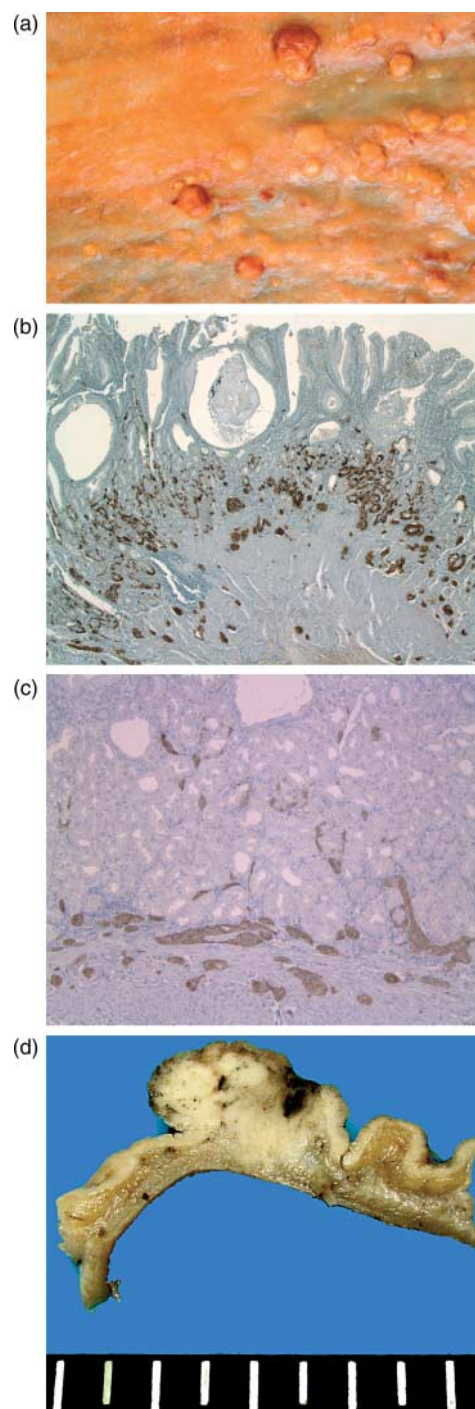
In general, the well-differentiated NENs are much more common (by a rate of  $\sim 10:0.5$ ) than the poorly differentiated NENs. However, at certain locations such as the oesophagus or the colon the poorly differentiated NENs are more frequent than their well-differentiated counterparts.

## Oesophagus

NENs of the oesophagus are extremely rare and therefore something special. Usually they present as large ulcerated poorly differentiated NECs in the lower third of the oesophagus and may, in addition, contain exocrine elements (Capella *et al.* 2000, Maru *et al.* 2008).

## Stomach

The stomach gives origin to three distinct types of well-differentiated NETs (Rindi *et al.* 1993) and also, but only rarely, to poorly differentiated NECs (Klöppel & Clemens 1996, Capella *et al.* 2000). The type 1 comprises 70–80% of all cases and occurs mainly in women at the age of 50–60 (Rindi *et al.* 1993, Scherübel *et al.* 2010). It is characterised by the occurrence of multiple small polypoid tumours (0.3–1 cm; Fig. 2a), which are composed of enterochromaffin-like (ECL) histamine-producing cells and are always associated



**Figure 2** Well-differentiated neuroendocrine neoplasms of the stomach: (a) multiple small polypoid tumours in the corpus region of the stomach associated with chronic atrophic gastritis of the oxyntic mucosa (type 1 gastric NET). (b) ECL cell hyperplasia in the oxyntic mucosa with microtumours. (c) ECL cell hyperplasia in patients with MEN1. (d) Type 3 NEN of the stomach with infiltration of muscular wall.

with autoimmune chronic atrophic gastritis of the oxyntic mucosa. This disease leads to the disappearance of the specific glands of the oxyntic mucosa harbouring the parietal cells. The consequences of the loss of parietal cells are insufficient production of intrinsic factor triggering pernicious anaemia via the decreased resorption of vitamin B12 and deficient production of gastric acid that stimulates the antral G cells to persistent hypersecretion of gastrin. It is thought that the hypergastrinaemia promotes the growth of the ECL cells of the oxyntic mucosa so that diffuse to micronodular ECL cell hyperplasia develops (Fig. 2b) and is followed by multiple ECL neoplasms after a latent period of many years (Bordi *et al.* 1998). The prognosis of these tumours is excellent, because they are usually G1 – NETs and so small when detected that they can be completely removed endoscopically. Metastasising type 1 gastric NETs may occasionally be observed, if the tumours are larger than 2 cm in size, infiltrate the muscularis propria, are angioinvasive and/or show G2 grade (Rappel *et al.* 1995).

Type 2 gastric NETs are very similar to type 1 NETs regarding cellular composition (ECL-tumours) and multifocality, but occur in the setting of MEN1, that is associated with a Zollinger–Ellison syndrome (ZES). They affect men and women equally (Scherübl *et al.* 2010). As patients with ZES but without MEN1 usually do not develop type 2 gastric NETs, the genetic changes associated with MEN1 are probably needed for tumour development (Debelenko *et al.* 1997). The tumour-free oxyntic mucosa shows ECL cell hyperplasia, but is not atrophic as in type 1 gastric NETs (Fig. 2c). Lymph node metastases are found more often than in type 1 NETs, since type 2 NETs are often more advanced in terms of size, muscular wall infiltration and angioinvasion than type 1 gastric NETs (Solcia *et al.* 1989).

Type 3 gastric NETs are solitary tumours that develop unrelated to chronic atrophic gastritis or MEN1. They occur mainly in men, at a mean age of 55 years (Scherübl *et al.* 2010). In most cases type 3 NETs are composed of ECL cells, while EC (serotonin) cell or gastrin cell tumours are extremely rare (Klöppel & Clemens 1996). Histologically, they are well differentiated, show a trabecular to solid pattern and in at least one-third of the patients, the tumour is already larger than 2 cm at the time of diagnosis (Fig. 2d), has invaded the muscular layer, shows angioinvasion, and/or has a proliferation rate exceeding 2–5%. In those type 3 NETs metastases are very likely to be present (Rappel *et al.* 1995). In rare cases type 3 tumours may be associated with a so-called atypical

carcinoid syndrome, characterised by cutaneous flushing in the absence of diarrhoea, usually coupled with liver metastases and production of histamine and 5-hydroxytryptophan (Scherübl *et al.* 2010).

Poorly differentiated NECs of the stomach (type 4 gastric NENs) are more common in men than in women, aged between 60 and 70 years (Scherübl 2010). They present as a large ulcerated lump with symptoms similar to those of adenocarcinomas. Occasionally they harbour an adenocarcinoma component. Hormones cannot be demonstrated and there is no relationships to chronic atrophic gastritis, but in exceptional cases are associated with MEN1 (Bordi *et al.* 1997). At the time of diagnosis most of the tumours are already in an advanced stage (tumour diameter more than 4 cm) and show extensive metastasis (Bordi *et al.* 1997).

Recently, multiple large (up to 1.3 cm) ECL cell tumours were found in a background of ECL cell hyperplasia and parietal cell hyperplasia in patients with hypergastrinaemia, but without ZES (Ooi *et al.* 1995, Abraham *et al.* 2005). It was suggested that the development of these NETs is associated with an intrinsic acid secretion abnormality of the parietal cells.

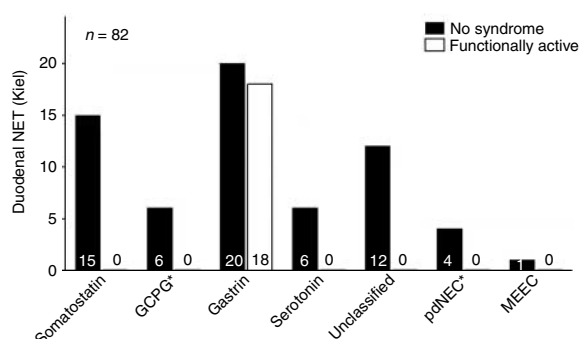
## Duodenum and upper jejunum

On the basis of their clinical, morphological, hormonal and genetic features several types have to be distinguished in the upper small intestine: gastrin-producing NETs with ZES (i.e. gastrinomas), gastrin-producing NETs without ZES, somatostatin-producing tumours with or without neurofibromatosis type 1 (NF1), serotonin- or calcitonin-producing NETs, gangliocytic paragangliomas and poorly differentiated NECs (Burke *et al.* 1990, Capella *et al.* 1995, Solcia *et al.* 2000, Jensen *et al.* 2006a,b, Klöppel *et al.* 2007; Fig. 3). These duodenal NENs can be divided into non-functioning and functioning neoplasms.

### Non-functioning NENs

These duodenal NENs are usually well differentiated and not associated with an inherited syndrome. Most of these tumours produce gastrin, followed by somatostatin, serotonin, pancreatic polypeptide and calcitonin. NECs are very rare and contain none of the usual hormones.

Gastrin-producing NETs are mainly localised in the proximal duodenum, are smaller than 2.0 cm and are limited to the mucosa–submucosa (Fig. 4). In these NETs, lymph node and distant metastases are rare (~5–10% of the cases (Oberhelman & Nelsen 1964, Donow *et al.* 1991, Jensen *et al.* 2006a)).



**Figure 3** Relative ratios of neuroendocrine tumours of the duodenum defined by their hormone expression. Neuroendocrine tumour archives of the Department of Pathology, University of Kiel, 1970 and 2006. Reproduced with kind permission from Springer Science+Media: *Virchows Archiv, Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors*, volume 451 supplement 1, ppS9–S27, Klöppel *et al.* (2007).

Somatostatin-producing NETs occur predominantly in the ampullary and periampullary region (Makhlouf *et al.* 1999, Garbrecht *et al.* 2008). If they involve the muscular wall, have a size >2 cm and an increased proliferation rate, the metastatic risk is >50%. However, even smaller tumours (between 1 and 2 cm or below) may show metastases in the paraduodenal lymph nodes. Approximately 20–30% of the somatostatin-producing tumours are associated with NF1 (Dayal *et al.* 1986b, Garbrecht *et al.* 2008). None of these somatostatin-producing NETs seem to develop the ‘somatostatinoma’ syndrome (diabetes mellitus, diarrhoea, steatorrhoea, hypo- or achlorhydria, anaemia and gallstones) that has been described in association with some pancreatic somatostatin-producing NETs (Garbrecht *et al.* 2008). The term somatostatinoma should therefore not be applied to these NETs, since, by definition, it denotes that the tumour is associated with the above mentioned syndrome.

Gangliocytic paragangliomas are characterised by their triphasic cellular differentiation (Fig. 5), consisting of neuroendocrine cells (producing somatostatin and/or pancreatic polypeptide), spindle-shaped Schwann-like cells, and ganglion cells. They usually occur in the periampullary region and follow a benign course. However, occasional, large tumours (size >2 cm) may spread to local lymph nodes, mainly attributable to the endocrine component of the lesion (Garbrecht *et al.* 2008).

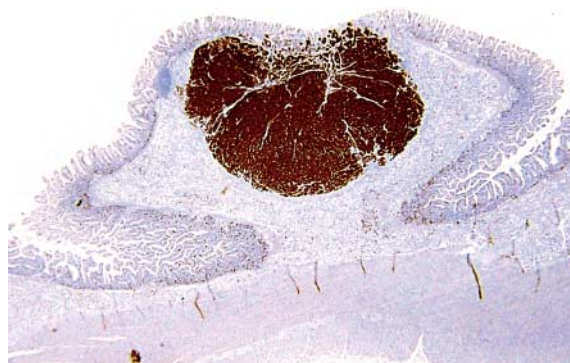
NECs occur primarily in or close to the ampullary region. They present in advanced stages, i.e. with lymph node, liver and other remote metastases (Zamboni *et al.* 1990, Nassar *et al.* 2005, Garbrecht *et al.* 2008).

## Functioning NENs

Approximately 50% of the sporadic (non-inherited) duodenal NETs that produce gastrin are functioning and associated with a ZES. These NETs are called gastrinoma. Twenty to 30% of the gastrinomas arise on a background of MEN1 (Anlauf *et al.* 2005, 2006a,b, 2007a,b, Jensen *et al.* 2006a, Klöppel *et al.* 2007). An important difference between sporadic and MEN1-associated gastrinomas is that the latter are invariably multicentric (Pipeleers-Marichal *et al.* 1990). Both, the sporadic and MEN1-associated gastrinomas frequently (50–90% of cases) metastasise to the regional lymph nodes, and these lymph node metastases are often much larger than the primary in the duodenum, that can be as small as 1 mm in size (Anlauf *et al.* 2008). The 10-year survival rate of patients with duodenal gastrinomas (59%) is significantly better than for patients with pancreatic gastrinomas (9%), probably because metastases to the liver are more frequent in pancreatic than duodenal gastrinomas and the local lymph node metastases seem to have little influence on survival. Serotonin-producing NETs causing a carcinoid syndrome are unusual in the duodenum.

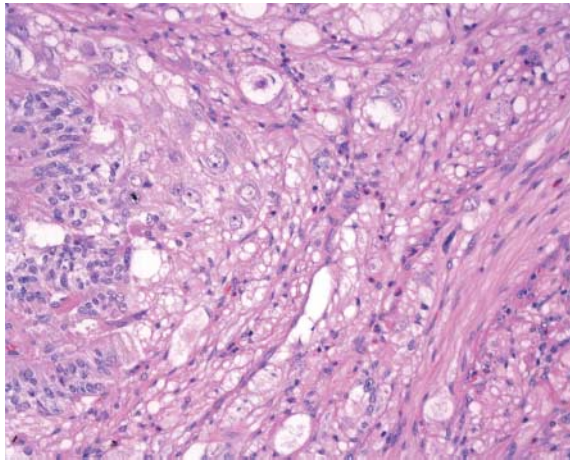
## Ileum

NETs usually present in the distal ileum close to the ileocecal valve in patients who are between 60 and 65 years old (Fig. 6a). They are not associated with any of the inherited syndromes (e.g. MEN1 or NF1), although familial cases have been observed and multicentricity occurs in 26–30% of the cases. In 15–29% they are associated with other non-carcinoid malignancies (Burke *et al.* 1997, Yantiss *et al.* 2003, Eriksson *et al.* 2008). The tumour structures are embedded in a sclerotic paucicellular stroma that may lead to kinking of the foregut and subsequently to bowel obstruction.



**Figure 4** Well-differentiated neuroendocrine tumour of the duodenum producing gastrin. Duodenal mucosa showing a small submucosal tumour.





**Figure 5** Gangliocytic paraganglioma showing triphasic cellular differentiation: Ganglion cells (center), endocrine cells (left) and Schwann cells (right).

Ileal NETs are well-differentiated serotonin-producing tumours (Fig. 6b). Although they usually have a low proliferation rate (Ki67 <2%), metastases to lymph nodes or even liver are common at the time of diagnosis. Below a tumour size of 0.5 cm they are infrequent, but in ileal NETs with a diameter of 1 cm, lymph node metastases are found in 30% of the patients, and above 2 cm, in 100% (Stinner *et al.* 1996).

Clinically, the tumours may be discovered by exploration of the gut, because they already gave rise to liver metastases or produced local symptoms (bowel obstruction, subileus) and/or a hormonal syndrome due to the effects of serotonin, called carcinoid syndrome. This is characterised by chronic diarrhoea, flush attacks, bronchial constrictions and (as a late event) right-sided heart failure due to valve sclerosis causing tricuspid regurgitation. The carcinoid syndrome is usually seen in patients with liver metastases (95%). Overall 5-year survival rates range from 50 to 60%, decreasing to 35% if liver metastases are present (Stinner *et al.* 1996).

Meckel's diverticulum is a rare site of NETs. These tumours, if found incidentally, are often still small (<1.7 cm) and have then rarely metastasised (Burke *et al.* 1997). However, if symptomatic, metastases are likely to be found (Modlin *et al.* 2005).

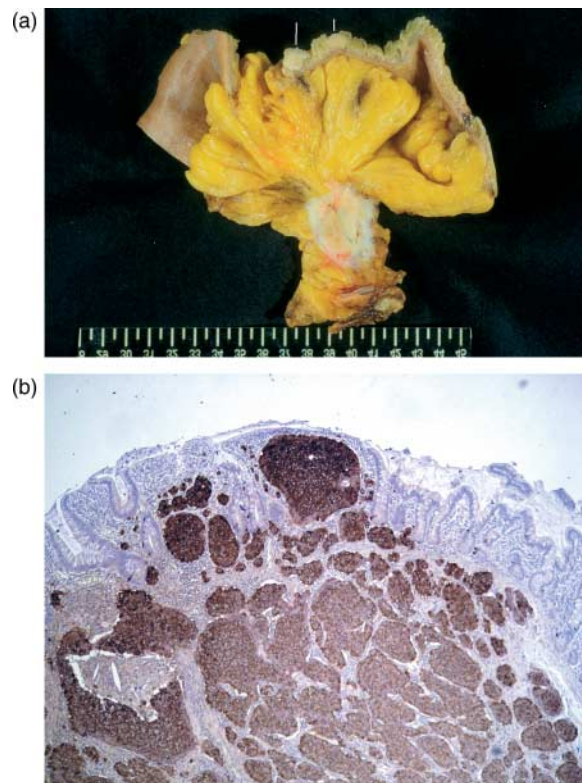
## Appendix

The tip of the organ is the preferred site of the appendiceal NETs that are mainly observed in women at an age of 40–50 years. Children may be also affected. The tumours are mostly between 1 and 2 cm

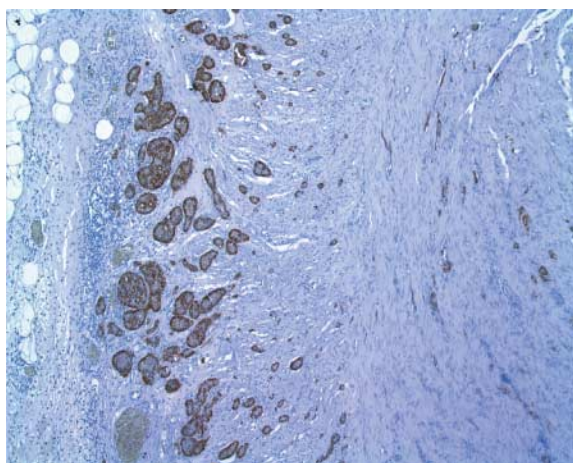
in size, infiltrate the appendix wall, are well differentiated and composed of serotonin-producing EC cells and net-like arranged S-100 cells (Fig. 7).

A size > 2 cm, a location at the base of the appendix, deep involvement of the mesoappendix and angioinvasion are potentially associated with metastases (McGory *et al.* 2005). The risk of lymph node metastases in tumours measuring 1–2 cm is 1% and increases to 30% in tumours measuring more than 2 cm (Stinner *et al.* 1996). Mesoappendix invasion is a debated variable (MacGillivray *et al.* 1992, Rossi *et al.* 2003). 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 (Parkes *et al.* 1993, Stinner *et al.* 1996). A NEC, as part of a mixed exocrine–endocrine carcinoma, has only been reported once so far (Klöppel *et al.* 2007).

Most tumours are detected because of symptoms of acute appendicitis. A carcinoid syndrome in association with a metastasised well-differentiated appendiceal NET is exceedingly rare (Moyana 1989).



**Figure 6** (a) Small neuroendocrine carcinomas (arrows) of the ileum with large lymph node metastasis in the mesentery. (b) The tumour infiltrates the muscular layer and produces serotonin.



**Figure 7** Well-differentiated serotonin-producing neuroendocrine carcinoma of the appendix with infiltration of the mesoappendix and angioinvasion.

### Colon and rectum

NETs are more frequent in the rectum than the colon, whereas NECs are more common in the colon (Anthony *et al.* 2010). The rectal NETs that are endoscopically detected are mostly small (<1 cm), movable submucosal tumours. They produce glucagon-like peptides and pancreatic polypeptide, but cause no hormonal syndrome. The few colonic NETs are also small, occur in the cecal region (except if they are associated with ulcerative colitis, Crohn's disease (West *et al.* 2007) and polypous colonic adenomas (Pulitzer *et al.* 2006)) and produce serotonin (Berardi 1972, Rosenberg & Welch 1985, Soga 1998). The NECs of the colon are usually large (>2 cm; Berardi 1972, Soga 1998) and have a high Ki67 index (Burke *et al.* 1991, Solcia *et al.* 2000, Crafa *et al.* 2003). Synchronous or metachronous colorectal carcinomas are frequently seen in association with NETs or NECs (Soga 1997, 1998).

Rectal and colonic NETs are often incidental findings at endoscopy. Tumour size significantly predicts malignant behaviour in NETs of the rectum, but also of the colon. Regional lymph node involvement is very likely, if they are larger than 2 cm and have invaded the muscular wall. In contrast, rectal NETs below 1 cm in size have a very low risk of lymph node metastasis, while those between 1 and 2 cm in size have a risk of 5%. If the tumours are poorly differentiated, there is a high rate of metastasis at the time of diagnosis (Brenner *et al.* 2004, 2007).

### Presacral region

A rare site of NENs is the presacral region between the rectum and the os sacrum (Horenstein *et al.* 1998,

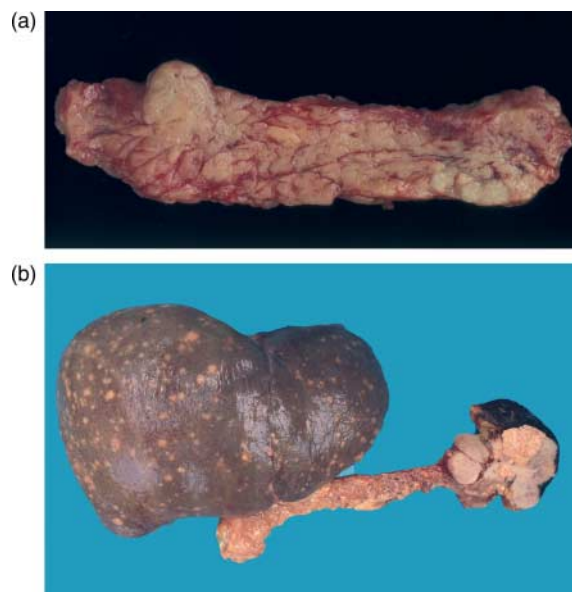
Theunissen *et al.* 2001). The NENs arising there are usually well differentiated, affect adults of both sexes and are frequently associated with tail gut cysts. Metastases may occur.

### Pancreas

Most PanNENs are solitary, well-demarcated and well-differentiated neoplasms (Heitz *et al.* 2004, Hruban *et al.* 2007, Klöppel *et al.* 2007). Their size ranges between 1 and 5 cm. Multiple tumours are rare and should always raise the suspicion of MEN1 or VHL.

Size (>2 cm), grossly infiltrative growth, metastases, angioinvasion and proliferative activity determine their prognosis and metastatic potential (Fig. 8). Recent studies provided evidence that this multi-parameter approach is a reliable tool for stratifying patients with PanNENs into risk groups (Capella *et al.* 1997, Heitz *et al.* 2004, Schmitt *et al.* 2007, Fischer *et al.* 2008, La Rosa *et al.* 2009, Scarpa *et al.* 2010).

PanNETs, i.e. the well-differentiated PanNENs, are divided into functioning and non-functioning tumours. The first group includes insulinomas, gastrinomas, glucagonomas, VIPomas and others. The second group, the non-functioning PanNETs, is observed more frequently than previously, although this probably does not reflect a true increase in number,



**Figure 8** Pancreatic neuroendocrine tumours: (a) tumour with a diameter of 2 cm (insulinoma without metastases), (b) large malignant tumour (>2 cm) in the head of the pancreas (malignant insulinoma with metastases). Reproduced with kind permission from Springer Science+Media: *Virchows Archiv*, Site-specific biology and pathology of gastroenteropancreatic neuroendocrine tumors, volume 451 supplement 1, ppS9–S27, Klöppel *et al.* (2007).



but rather improved diagnostic methods (Schmitt *et al.* 2007). In terms of relative frequency they represent at least 60% of all PanNETs. Both functioning and non-functioning NETs occur in adults, but with a wide age range (20–80 years). They are rare in children (Crain & Thorn 1949). Most PanNETs are sporadic, but some may occur in inherited disorders such as MEN1, VHL and NF1 (Anlauf *et al.* 2007a). PanNENs that are poorly differentiated (PanNECs) are rare (Solcia *et al.* 1997, Hruban *et al.* 2007).

#### *Insulinomas*

The vast majority of these tumours is between 0.5 and 2 cm in diameter and shows a benign behaviour (Solcia *et al.* 1997). This may be due in part to their early detection, as they already become symptomatic at a small size (Soga *et al.* 1998). Approximately 8–10% of insulinomas are larger than 2 cm in diameter and are then usually malignant (Stefanini *et al.* 1974, van Heerden *et al.* 1979, Service *et al.* 1991, Soga *et al.* 1998). Approximately 4–7% of patients with insulinomas suffer from MEN1 (Service *et al.* 1991) and very rarely from NF1 (Fung & Lam 1995, Perren *et al.* 2007).

#### *Gastrinomas*

Pancreatic gastrinomas are mostly solitary tumours, have a diameter of 2 cm or more and occur in the pancreatic head (Stabile *et al.* 1984, Donow *et al.* 1991, Pipeleers-Marichal *et al.* 1993). They are associated with the sporadic form of ZES and are less common than duodenal gastrinomas that are much smaller and quite often seen in the setting of MEN1 (Donow *et al.* 1991). The risk of lymph node and liver metastases increases with tumour size and metastasis and occurs with a frequency of 30% (Stamm *et al.* 1991, Solcia *et al.* 1997). In general, the progression of gastrinomas is relatively slow with a combined 5-year survival rate of 65% and a 10-year survival rate of 51% (Jensen & Gardner 1993). Even with metastatic disease a 10-year survival of 46% (lymph node metastases) and 40% (liver metastases) has been reported (O'Dorisio *et al.* 1993). Patients with complete tumour resection have 5- and 10-year survivals of 90–100%.

#### *Glucagonomas*

These are usually large, solitary tumours with a diameter between 3 and 7 cm, commonly occurring in the tail of the pancreas (Ruttman *et al.* 1980, Solcia *et al.* 1997). They produce a syndrome characterised by a necrolytic migratory erythema, mild glucose intolerance, anaemia and weight loss (Heitz *et al.* 2004).

Metastases to lymph nodes and the liver are found in ~60–70% of the cases at the time of diagnosis (Higgins *et al.* 1979, Ruttman *et al.* 1980, Prinz *et al.* 1981). Malignant glucagonomas tend to grow slowly and patients may survive for many years.

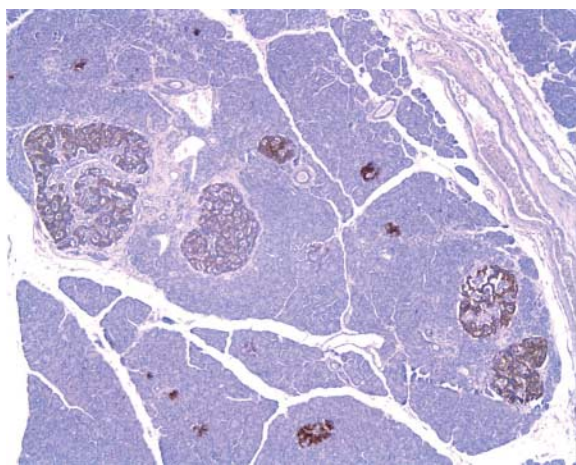
#### *VIPomas*

VIP expressing NETs are preferentially located in the pancreatic tail, are large and single tumours (Capella *et al.* 1983) and have commonly (60–80%) led to metastases in the lymph nodes and the liver at the time of diagnosis (Martin & Potet 1974). VIP secretion produces the watery diarrhoea (up to 20 l/day), hypokalemia, hypochlorhydria and alkalosis (Verner–Morrison) syndrome. The 5-year survival rate is about 59% for patients with metastases and 94% for those without metastases (Heitz *et al.* 2004). In adults these tumours are located in the pancreas, in children they occur extrapancreatic and present as ganglioneuromas (Heitz *et al.* 2004).

Somatostatin-producing NETs are rare in the pancreas and in ~50% of the cases malignant (Stamm *et al.* 1986, Capella *et al.* 1991, Garbrecht *et al.* 2008). Because some patients presented with symptoms attributed to the inhibitory effects of somatostatin on the function of various cell systems and including diabetes mellitus, cholecystolithiasis, steatorrhoea, indigestion, hypochlorhydria and occasionally anaemia, a somatostatinoma syndrome was defined (Larsson *et al.* 1977, Krejs *et al.* 1979, Pipeleers *et al.* 1983, Vinik *et al.* 1987, Sessa *et al.* 1998). However, the recent literature does not contain any convincing report on a somatostatinoma syndrome, although somatostatin-producing NETs have been identified not only in the pancreas but also at other sites, particularly the duodenum (Dayal *et al.* 1986a,b, Taccagni *et al.* 1986, Garbrecht *et al.* 2008). Therefore, doubts have been expressed regarding the existence of a somatostatinoma syndrome and the question has been raised whether the described symptoms were non-specific manifestations of large malignant pancreatic NETs, that happened to produce somatostatin (Garbrecht *et al.* 2008). The last view is supported by the results in a series of 386 PanNENs, collected between 1972 and 2006, which contains ten well-differentiated somatostatin-producing PanNENs, none of which being associated with the so-called somatostatinoma syndrome (Garbrecht *et al.* 2008).

#### *Very rare functioning PanNETs*

They include ACTH positive NETs causing Cushing's syndrome (Heitz *et al.* 1981, Clark & Carney 1984,



**Figure 9** Insulinomatosis of the pancreas showing multiple microtumours staining for insulin.

Melmed *et al.* 1987), GHRH positive NETs causing acromegaly (Berger *et al.* 1984, Bostwick *et al.* 1984, Dayal *et al.* 1986a, Sano *et al.* 1988), calcitonin positive NETs causing diarrhoea (Drucker *et al.* 1989, Kao *et al.* 1990) and serotonin positive NETs causing a carcinoid syndrome (Wilander *et al.* 1981). Many of these neoplasms are solitary and large and have metastasised to the liver and lymph nodes when detected. The prognosis is therefore usually poor (Heitz *et al.* 2004).

**Non-functioning PanNETs**

In early series these tumours were usually large when detected (5–6 cm) and frequently malignant (Kent *et al.* 1981). Recently, however, smaller non-functioning tumours are increasingly recognised by modern

imaging techniques (Schmitt *et al.* 2007). These neoplasms are either incidentally detected or become symptomatic due to size, invasion of adjacent organs or the occurrence of metastases. Large non-functioning PanNETs are reported to occur most frequently in the head of the pancreas, possibly because they are most likely to produce cholestasis in this location. Immunohistochemically, they often express various hormones (Kapran *et al.* 2006) and some of them are associated with elevated hormone levels in the blood, reflecting the hormonal immunoreactivity in the tumour. A special histologic feature of glucagon-producing NETs is grossly cystic changes (Yagihashi *et al.* 1992, Ligneau *et al.* 2001, Konukiewicz *et al.* 2011). Serotonin expressing PanNETs are characterised by a trabecular pattern, with tumour cell cords embedded in a sclerotic stroma, and a localisation next to the main pancreatic duct which may cause duct obstruction (McCall *et al.* 2011, Walter *et al.* 2011).

Non-functioning PanNECs of the pancreas showing a diffuse infiltrative growth pattern, multiple small necrosis and either small- to medium-sized cells or large cells with a distinct nucleolus have a high mitotic rate and proliferative activity of more than 20% (Solcia *et al.* 1997).

The 5-year survival rate in non-functioning PanNETs is ~65% and the 10-year survival rate 45%. Follow-up in patients with PanNETs having a diameter of <2 cm revealed that they are mostly cured by surgery (Schmitt *et al.* 2007).

Single tumours that are smaller than 0.5 cm (microadenomas) are grossly difficult to detect. They are therefore incidental findings, either at autopsy or in resection specimens removed because of other larger

**Table 3** Proposal for the stratification of gastroenteropancreatic neuroendocrine tumours into three treatment groups based on growth features, TNM stages and grade

Prognosis	Histological type	Grade	Stage	Potential treatment
Localised tumour				
Very low risk of metastasis	Well differentiated	G1	T1	Endoscopic resection
Low risk	Well differentiated	G1	T2	Surgery
Intermediate risk	Well differentiated	G2	T1	Surgery
High risk	Well differentiated	G1/2	T2	Surgery
High risk	Poorly differentiated	G3	T1/2/3	Surgery, a.t.
Nodal metastases				
Slow growth	Well differentiated	G1	T1/2/3 N1	Surgery
Intermediate growth	Well differentiated	G2	T1/2/3 N1	Surgery, a.t.
Fast growth	Poorly differentiated	G3	T1/2/3 N1	Surgery, a.t.
Nodal and hematogenous metastases				
Slow growth	Well differentiated	G1	Any T N1M1	Surgery, a.t.
Intermediate growth	Well differentiated	G2	Any T N1M1	Surgery, a.t.
Fast growth	Poorly differentiated	G3	Any T N1M1	Chemotherapy

a.t., additional treatment, including biotherapy and/or chemotherapy.

tumours or chronic pancreatitis. Histologically, they show a trabecular pattern and usually express glucagon.

Pancreatic microadenomatosis (in addition to individual NETs larger than 0.5 cm) is a typical finding in inherited conditions such as the MEN1 syndrome (Anlauf *et al.* 2006a,b, 2007a,b) and the VHL disease (Perigny *et al.* 2009). VHL patients develop non-functioning PanNETs in 12–17% of the cases (Lubensky *et al.* 1998). Recently, two other conditions have been described, in which multiple insulin (Anlauf *et al.* 2009) or glucagons-producing tumours (Henopp *et al.* 2009) develop from microadenomas in the pancreas. While the first condition, called insulinomatosis (Fig. 9), is characterised by recurrent insulinoma syndrome if only the visible and palpable tumours are resected, glucagon cell adenomatosis is usually nonsyndromatic. The latter condition was found to harbour a mutation of the glucagon receptor gene (Zhou *et al.* 2009).

## Treatment

The improved and standardised clinicopathologic diagnostics using the WHO (see Table 1) and TNM classifications for GEP-NEN categorisation allow a refined prognostic stratification. This has led to new therapeutic guidelines (Plöckinger & Wiedemann 2007). Table 3 shows, how the treatment of the patients with GEP-NENs can be adjusted to growth and stage of the individual tumour.

## Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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