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Gastroenteropancreatic Neuroendocrine Neoplasms. Classification and Diagnostic Criteria

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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 tumors that generate steroid hormones. The tumors 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 recognize 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 tumors (Klöppel et al. 2009). Under the electron microscope the NENs show typical neurosecretory granules.

This review deals with the classification of the gastroenteropancreatic neuroendocrine neoplasms (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 et al. 2004). Only 8 of the 15 hormones that were identified in the cells of the gastrointestinal tract have so far been recognized in GEP-NENs. Many of these hormones give rise to hormonal syndromes, if they are produced and secreted by the majority of the tumor cells. The GEP-NENs that are associated with hormonal syndromes are then called insulinomas, glucagonomas, gastrinomas and seretoninomas. In addition, there are GEP-NENs which produce hormones that are ectopic to the GEP system such as vasoactive intestinal polypeptide (VIP), adrenocorticotropical hormone (ACTH) or growth hormone releasing factor (GHRF). 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 recognized in the gastrointestinal tract and the pancreas differ

considerably in their metastasizing capacity (i.e. their behavior). 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 tumors derive. It has therefore always been difficult to classify the GEP-NENs. In 1963, Williams and Sandler classified the GEP-NENs by embryological origin as foregut (stomach, duodenum, upper jejunum and pancreas), midgut (lower jejunum, ileum, appendix and cecum) and hindgut (colon and rectum) tumors and found considerable clinicopathological differences between the three groups (Williams, Sandler 1963). However, with the recognition of many new GEP-NEN entities in the last two decades, especially among the foregut tumors, 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 behavior of GEP-NENs (Capella et al. 1995). As a first step it distinguished between pure endocrine tumors and mixed endocrine-exocrine tumors. In a second step a uniform scheme of classification was applied to all pure GEP-NENs, identifying three tumor categories, irrespective of their site of origin (see Table 1):

(1) well differentiated endocrine tumors with probably benign behavior,
(2) well differentiated endocrine tumors (WDETs) with uncertain behaviour and well differentiated endocrine carcinomas (WDECs) with low grade malignant behavior, and
(3) poorly differentiated endocrine carcinomas (PDECs) with high grade malignant behavior.

In a third step, the well differentiated, low-grade-proliferative GEP-NENs which are also called carcinoids in the gastrointestinal tract (Oberndorfer 1907) or islet cell tumors 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 tumor extension, angioinvasion, proliferative activity (Ki67 index) and their syndromatic features (Solcia et al. 2000, Heitz et al. 2004). They were characterized 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 malignant. They were characterized 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 in order 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 which contained site-specific TNM-classifications (Rindi et al. 2006, Rindi et al. 2007). In addition, a three-tiered grading system of GEP-NENs based on mitotic count and Ki-67 index (Rindi et al. 2006, Rindi et al. 2007) and a standardized diagnostic procedure were suggested (Klöppel et al. 2009). Both grade 1 (Ki67 index < 2%) and grade 2 (Ki67 index 2% - 20%) neuroendocrine neoplasms are considered well-differentiated tumors, whereas grade 3 (Ki67 index > 20%) characterizes the poorly differentiated tumors. Both the staging proposal and the grading system were recently validated for forgut and particularly pancreatic NENs 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 7th edition of the AJCC/UICC (Sobin et al. 2009) contains a TNM classification of well differentiated 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 cell) neuroendocrine carcinomas 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. Second, the term “neuroendocrine neoplasm” encompasses all well and poorly differentiated tumors of the neuroendocrine cells. Third, the pure neuroendocrine neoplasms of the gastrointestinal tract and pancreas are stratified into two groups (Table 1): (1) the well differentiated neuroendocrine tumors, called NETs, and (2) the poorly differentiated neuroendocrine carcinomas, called NECs. The NETs are then separated by their proliferative activity into either G1 (equivalent to carcinoids) or G2 NETs. The NECs, that are G3 tumors, are subtyped into small cell and large cell neoplasms (see

Table 1). TNM-staging of tumor extension according to tumor 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 tumor cells) non-endocrine components (usually adenocarcinoma structures) are distinguished from the pure neuroendocrine neoplasms and called mixed adeno-neuroendocrine carcinomas (Table 1).

Pathology

Distribution and Relative Frequency

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 approximately 10:0.5) than the poorly differentiated NENs. However, at certain locations such as the esophagus or the colon the poorly differentiated NENs are more frequent than their well differentiated counterparts.

Esophagus

NENs of the esophagus are extremely rare and therefore something special. Usually they present as large ulcerated poorly differentiated NECs in the lower third of the esophagus 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 (Capella et al. 2000, Klöppel, Clemens 1996).The type 1 comprises 70-80% of all cases and occurs mainly in women at the age of 50 to 60 (Rindi et al. 1993, Scherübl et al. 2010). It is characterized by the occurrence of multiple small polypoid tumors (0.3–1 cm), that are composed of ECL (enterochromaffin-like histamine-producing) cells and are always associated with autoimmune chronic atrophic gastritis of the oxyntic mucosa. This disease 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 insufficient production of intrinsic factor triggering 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 the hypergastrinemia promotes the growth of the ECL cells of the oxyntic mucosa so that diffuse to micronodular ECL cell hyperplasia develops and is followed by multiple ECL neoplasms after a latent period of many years, (Bordi et al. 1998). The prognosis of these tumors is excellent, because they are usually G1 – NETs and so small when detected that they can be completely removed endoscopically. Metastasizing Type 1 gastric NETs may occasionally be observed, if the tumors 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-tumors) and multifocality, but occur in the setting of multiple endocrine neoplasia type 1 (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 tumor development (Debelenko et al. 1997). The tumorfree oxyntic mucosa shows ECL-cell hyperplasia, but is not atrophic as in type 1 gastric NETs. 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 tumors 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 tumors are extremely rare (Klöppel and Clemens 1996). Histologically, they are well differentiated, show a trabecular to solid pattern and in at least one third of the patients, the tumor is already larger than 2 cm at the time of diagnosis, 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 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 (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 to 70 years (Scherübl 2010). They present as a large

ulcerated lump with symptoms similar to those of adenocarcinomas. Occasionally they harbor an adenocarcinoma component. Hormones cannot be demonstrated and there is no relationship to chronic atrophic gastritis, but in exceptional cases are associated with MEN1 (Bordi et al. 1997). 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 (Bordi et al. 1997).

Recently, multiple large (up to 1.3 cm) ECL-cell tumors were found in a background of ECL-cell hyperplasia and parietal cell hyperplasia in patients with hypergastrinemia, 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 testine: 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, gangliocytic paragangliomas and poorly differentiated neuroendocrine carcinomas (Burke et al. 1990, Capella et al. 1995, Solcia et al. 2000, Klöppel et al. 2007). These duodenal NENs can be divided into nonfunctioning and functioning neoplasms.

Nonfunctioning NENs:

These duodenal NENs are usually well-differentiated and not associated with an inherited syndrome. Most of these tumors 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 localized in the proximal duodenum, are smaller than 2.0 cm and are limited to the mucosa-submucosa. In these NETs, lymph node and distant metasases are rare (approximately in 5 to 10% of the cases (Oberhelman and Nelsen 1964, Donow et al. 1991, Jensen et al. 2006).

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 greater than 2 cm and an increased proliferation rate, the metastatic risk is greater than 50 %. However, even smaller tumors (between 1 and 2 cm or below) may show metastases in the paraduodenal lymph nodes. Approximately 20 – 30 % of the somatostatin producing tumors are associated with neurofibromatosis type 1 (Dayal et al. 1986, 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 applied to these NETs, since, by definition, it denotes that the tumor is associated with the above mentioned syndrome.

Gangliocytic paragangliomas are characterized by their triphasic cellular differentiation, 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, Garbrecht et al. 2008, Nassar et al. 2005).

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, Anlauf et al. 2006, Jensen, Niederle 2006, Anlauf et al. 2007, 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) metastasize 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 1mm 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. They are not associated with any of the inherited syndromes (e.g. MEN1 or neurofibromatosis type 1), 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 tumor structures are embedded in a sclerotic paucicellular stroma that may lead to kinking of the foregut and subsequently to bowel obstruction. Ileal NETs are well differentiated serotonin producing tumors. Athough they usually have a low proliferation rate (Ki-67 < 2%), metastases to lymph nodes or even liver are common at the time of diagnosis. Below a tumor 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 tumors 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 characterized by chronic diarrhea, 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 50-60%, decreasing to 35% if liver metastases are present (Stinner et al 1996).

Meckel's diverticulum is a rare site of NETs. These tumors, if found incidentally, are often still small (< 1.7 cm) and have then rarely metastasized (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 which are mainly observed in women at an age of 40 to 50 years. Children may be also affected. The tumors are mostly between 1-2 cm in size, infiltrate the appendix wall, are well differentiated. and composed of serotonin-producing EC cells and net-like arranged S-100 cells.

A size greater than 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 tumors measuring 1 to 2 cm is 1% and increases to 30% in tumors 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 (Rossi et al. 2004).

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

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 tumors. 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 (Matsumoto et al. 2003, 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, Soga 1998).

Rectal and colonic NETs are often incidental findings at endoscopy. Tumor size significantly predicts malignant behavior 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 beween 1 and 2 cm in size have a risk of 5%. If the tumors are poorly differentiated, there is a high rate of metastasis at the time of diagnosis (Brenner et al. 2004, Brenner et al. 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 pancreatic NENs (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 cm and 5 cm. Multiple tumors 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. 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 tumors. 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, 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 to 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 (Perren et al. 2006). PanNENs that are poorly differentiated (PanNECs) are rare (Solcia et al 1997, Hruban et al 2007).

Insulinomas: The vast majority of these tumors are between 0.5 and 2 cm in diameter and show a benign behavior (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 to 10 % of insulinomas are larger than 2 cm in diameter and are then usually malignant (Service et al. 1991, Soga et al. 1998, Stefanini et al. 1974, van Heerden et al. 1979). 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. 2006).

Gastrinomas: Pancreatic gastrinomas are mostly solitary tumors, 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 which 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 tumor 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% amd 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 tumor resection have 5- and 10-year survivals of 90-100%.

Glucagonomas: These are usually large, solitary tumors with a diameter between 3 and 7 cm, commonly occurring in the tail of the pancreas (Ruttmann et al. 1980, Solcia et al. 1997). They produce a syndrome characterized by a necrolytic migratory erythema, mild glucose intolerance, anemia and weight loss (Heitz et al. 2004). Metastases to lymph nodes and the liver are found in approximately 60-70% of the cases at the time of diagnosis (Higgins et al. 1979, Prinz et al. 1981, Ruttmann et al. 1980). Malignant glucagonomas tend to grow slowly and patients may survive for many years.

VIPomas: Vasoactive intestinal polypeptide (VIP) expressing NETs are preferentially located in the pancreatic tail, are large and single tumors (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 and Potet 1974). VIP secretion produces the watery diarrhea (up to 20 liters a 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 tumors 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 approximately 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, steatorrhea, indigestion, hypochlorhydria and occasionally anemia, a somatostatinom syndrome was defined (Kreis et al. 1979, Larsson et al. 1977, Pipeleers et al. 1983, Sessa et al. 1998, Vinik et al. 1987). 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. 1986, Garbrecht et al. 2008, Taccagani et al. 1986). Therefore doubts have been expressed regarding the existence of a somatostatinoma syndrome and the question has been raised whether the described symptoms were nonspecific 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 pancreatic NENs, collected between 1972 and 2006, which contains 10 well differentiated somatostatin producing pancreatic NENs,

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

Nonfunctioning PanNETs: In early series these tumors were usually large when detected (5 – 6 cm) and frequently malignant (Kent et al. 1981). More recently, however, smaller nonfunctioning tumors are increasingly recognized 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 nonfunctioning 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 tumor. A special histologic feature of glucagon-producing NETs are grossly cystic changes (Yagihashi et al. 1992, Ligneau et al. 2001, Konukiewitz et al 2011**)**. Serotonin expressing PanNETs are characterized by a trabecular pattern, with tumor cell cords embedded in sclerotic stroma, and a localization next to the main pancreatic duct, that may cause duct obstruction (McCall et al 2011).

Nonfunctioning 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 nonfunctioning PanNETs is approx. 65% and the 10-year survival rate 45%. Follow-up in patients with PanNETs having a diameter of less than 2 cm revealed that they are mostly cured by surgery (Schmitt et al. 2007).

Single tumors 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 tumors 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. 2006, Anlauf et al. 2007) and the VHL disease (Perigny et al. 2009). VHL patients develop nonfunctioning 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 glucagon producing tumors (Henopp et al. 2009) develop from microadenomas in the pancreas. While the first condition, called insulinomatosis, is characterized by recurrent insulinoma syndrome if only the visible and palpable tumors are resected, glucagon cell adenomatosis is usually nonsyndromatic. The latter condition was found to harbor a mutation of the glucagon receptor gene (Zhou et al. 2009).

Treatment

The improved and standardized clinicopathologic diagnostics using the WHO (see Table 1) and TNM classifications for GEP-NEN categorization allow a refined prognostic stratification. This has lead 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 tumor.

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Table 1:

Comparison of the WHO classification 2010 for gastroenteropancreatic neuroendocrine neoplasms with previous WHO classifications.

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

G, Grade (for definition, see text)

*In case that the Ki67 proliferation rate exceeds 20%, this NET may be graded G3.

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

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	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, A. mesent. sup.)

Table 3

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

Prognosis	**Histological type**	**Grade**	**Stage**	**Potential treatment**
Localized tumor				
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