Endocrine Neoplasia

20

20.1 Terminology and Classification

This group of pancreatic neoplasms is characterized by a predominant neuroendocrine differentiation. Over the years, the terminology and classification of endocrine neoplasia arising in the pancreas has undergone multiple changes. The most recent alterations were introduced in 2019 by the 5th edition of the WHO classification of tumors of the digestive system [1], ten years after the 4th edition [2] and 15 years after the WHO classification of tumors of endocrine organs [3] had been published.

The term 'carcinoid' is outdated and confusing, because it is often used in a more general sense than its original meaning of a serotonin-producing well-differentiated endocrine tumor. The term "islet cell tumor" has also been used previously. 'Neuroendocrine tumor' or 'neuroendocrine neoplasm' seem to be more appropriate terms, as they refer to the histogenesis of these tumors only, without connotations regarding the grade of tumor differentiation or hormonal production. 'Endocrine tumor' is preferred by some, because the prefix 'neuro-'refers back to the time when endocrine cells in the digestive system were believed to be derived from the neuroectodermal crest. However, sufficient features are shared between the endocrine and neural system to justify this prefix, and both 'endocrine' and 'neuroendocrine' are currently used interchangeably.

According to the WHO classification 2010 [2], pancreatic neuroendocrine neoplasms were divided into the two main categories of neuroendocrine tumors (PanNETs) and neuroendocrine carcinomas (PanNECs), whereby PanNETs could be further distinguished as grade 1 and grade 2 tumors. PanNETs differ from PanNECs morphologically, genetically, clinically, and epidemiologically. Overall, PanNETs are by far the most common entity within the group of pancreatic neuroendocrine neoplasms. They are characterized by an indolent clinical course and a typical organoid microscopic growth pattern. Their proliferative activity covers a range from <1% to up to 20%, and the tumors frequently harbor mutations in the *MEN1*, *DAXX*, and *ATRX* genes. In contrast, PanNECs are rare, highly aggressive tumors that despite a good response to platinum-based chemotherapy are associated with poor survival. They do not exhibit an organoid growth pattern on microscopic examination and show a high proliferative activity (>20%) that often lies in the range of 70–90%. They are associated with mutation of *TP53* and inactivation of the RB1/p16 pathway, and lack the mutations that are found frequently in PanNETs. Taken together, PanNECs share with PanNETs the expression of neuroendocrine markers, but they are not closely related neoplasms. PanNECs do not usually arise in association with PanNETs.

In 2019, the new WHO classification [1] introduced a new entity, PanNET grade 3, based on

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the concept that well-differentiated neuroendocrine neoplasms can be high-grade. Indeed, growing evidence shows that neuroendocrine tumors with morphological features similar to those of grade 1 and grade 2 PanNETs but with a higher proliferative activity that falls into the range of PanNECs (Ki67 index >20%) show clinical and genetic features that are more akin PanNETs than PanNECs. To avoid confusion with the newly introduced entity of PanNET grade 3, PanNECs are no longer assigned a grade, since all PanNECs are high-grade.

The term mixed adenoneuroendocrine carcinoma (MANEC) has been substituted by the category of mixed neuroendocrine—non-neuroendocrine neoplasms (MiNENs), which now encompasses a broader range of mixed neoplasms, including also tumors with squamous carcinoma or PanNET as a component of the neoplasm. The term MiNEN refers to an overarching diagnostic category that for the diagnosis of an individual tumor needs to be supplemented with the description of the exact nature of both tumor components.

The rationale for the change in classification and the defining criteria of the various categories are discussed in detail in this chapter. Table 20.1 provides a comparison between the WHO classification systems of 2010 and 2019.

Table 20.1 Comparison of terminology for pancreatic neuroendocrine neoplasia used by the WHO classifications 2010 and 2019

WHO 2010	WHO 2019
1. PanNET *grade 1*	1. PanNET *low-grade (grade 1)*
2. PanNET *grade 2*	2. PanNET *intermediate-grade (grade 2)*
	3. PanNET *high-grade (grade 3)*
3. PanNEC grade 3 (large or small cell type)	4. PanNEC (large or small cell type) *high-grade*
Mixed adenoneuroendocrine carcinoma (MANEC)	Mixed neuroendocrine—non-neuroendocrine neoplasm (MINEN) *variable grade*

Adapted from [1, 2]
Abbreviations: *PanNEC* pancreatic neuroendocrine carcinoma, *PanNET* pancreatic neuroendocrine tumor

20.2 Epidemiology

Pancreatic neuroendocrine neoplasms are rare, and they represent only 2–5% of all pancreatic tumors. Within the group of pancreatic endocrine tumors, PanNETs grade 1–3 are by far the most common, whereas PanNECs are rare and constitute <1% of all pancreatic tumors and 2–3% of all pancreatic endocrine neoplasms. The incidence of PanNETs in the general population is less than 1/100,000. Post mortem studies report a higher incidence (up to 1.5% of unselected autopsies), which results from the fact that PanNETs may remain occult during life, especially if they are small (<1 cm diameter) and hormonally inactive. A mild increase in incidence over recent years may be due to increased awareness and an improved detection rate both by imaging and laboratory testing. Within the group of sporadic functioning PanNETs, insulinoma is the most frequent (approximately 70% of all pancreatic neuroendocrine neoplasms). While there is no sex predilection for PanNETs, PanNECs are diagnosed slightly more frequently in males than in females. The age range is wide for PanNETs, with most patients being between 30 and 60 years old. Patients with PanNEC are usually 50–60 years of age, but younger individuals may also be affected.

While very little is known about risk factors for sporadic pancreatic endocrine neoplasia, the genetics of syndromic PanNETs in multiple endocrine neoplasia (MEN) type 1 and type 4, von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) are well established. Recently, a few kindreds with insulinomatosis have been reported (see Sect. 20.14).

20.3 Clinical Features

Clinically, the distinction between functioning and nonfunctioning PanNETs is important. *Functioning PanNETs* are associated with a clinical syndrome related to the inappropriate hormone release by the tumor. Table 20.2 summarizes the key features of the most common functioning

Table 20.2 Functioning pancreatic neuroendocrine tumors, in descending order of relative incidence

	Incidence (%)	Localization	Clinical presentation	Morphological features	Genetics	Prognosis
Insulinoma	• 27% of all PanNETs • Most frequent among functioning PanNETs (42%) • 0.4 cases/100,000 person-years	• <2% in duodenum • Extremely rare in small bowel, splenic hilum, stomach, lung, cervix, ovary	Whipple triad: 1. Symptoms of hypoglycemia: • Neurological: diplopia, blurred vision, confusion, abnormal behavior, amnesia, coma, focal seizures • Autonomic nervous response: sweating, weakness, hunger, tremor, nausea, anxiety, palpitation 2. Plasma glucose <2.2 mmol/l 3. Symptom relief upon intake of glucose	• Macroscopy: Size: 0.5–11 cm, 75% 0.5–2 cm; 10% are multiple, syn-/metachronous • Microscopy: amyloid uncommon but relatively characteristic; may contain psammoma bodies	• 4–7% associated with MEN 1 • Rare reports of association with insulinomatosis	2–18% malignant
Gastrinoma	• Up to 30% of functioning PanNETs • 4–8% of all PanNETs	• 25% pancreatic • 70% duodenal (mainly in 1st and 2nd part) • Rare in stomach, small bowel, bile duct, liver, kidney, mesentery, heart • Primary existence in peripancreatic/ periduodenal lymph nodes questioned	Zollinger-Ellison syndrome: • Duodenal ulcer • Gastro-esophageal reflux disease • Abdominal pain • Diarrhea • ECL-like cell hyperplasia/ neoplasia in gastric fundus	• Macroscopy: – Pancreatic: most >2 cm – duodenal: most <1 cm, confined to (sub-)mucosa – Lymph node metastasis may be larger than primary tumor • Microscopy: As in other PanNETs	• 25% associated with MEN 1 (predominantly duodenal SSToma) • Rare reports on association with NF1, NF2 and TSC	• Usually malignant • Liver metastasis in 22–35% of pancreatic gastrinomas • Liver metastasis in 0–10% of duodenal gastrinomas
VIPoma	3–8% of all PanNETs	• 80% pancreatic • Rarely in extrapancreatic location: small bowel, esophagus, kidney • Neurogenic VIP-secreting tumors in sympathetic ganglia and adrenal glands	WDHA syndrome (Verner-Morrison syndrome): • Watery diarrhea (large volume) • Hypokalemia • Achlorhydria/hypochlorhydria • Acidosis	• Macroscopy: – Size: 2–20 cm (mean: 4.5 cm) • Microscopy: As in other PanNETs	10% associated with MEN 1	Approximately 50–80% present with distant metastasis (mainly liver)

(continued)

Table 20.2 (continued)

	Incidence (%)	Localization	Clinical presentation	Morphological features	Genetics	Prognosis
Glucagonoma	• 1–2% of all PanNETs • 8–13% of functioning PanNETs	• Extremely rare outside pancreas • Predilection for pancreatic tail	Glucagonoma syndrome (% of patients): • Necrolytic migratory erythema (70%), stomatitis, cheilitis, alopecia, vulvovaginitis, urethritis • Mild glucose intolerance (50%) • Normochromic/normocytic anemia (33%) • Weight loss (65%) • Depression (20%) • Diarrhea (20%) • Deep venous thrombosis (10–15%)	• Macroscopy: Usually large (mean diameter: 7 cm) • Microscopy: As in other PanNETs	• <5% associated with MEN 1 (but nonfunctioning PanNETs with immunoreactivity for glucagon common in MEN 1) • Rare reports on association with glucagon cell hyperplasia and neoplasia	Mostly malignant, 60–70% present with metastasis
Somatostatinoma (SSToma)	2% of all PanNETs	• Pancreatic head more commonly involved than body or tail • Also in duodenum and ampulla	SSToma syndrome: • Diabetes mellitus/glucose intolerance • Hypochlorhydria • Gallbladder disease (stones, reduced motility) • Diarrhea, steatorrhea • Anemia • Weight loss Duodenal SSTomas are rarely associated with SSToma syndrome	• Macroscopy: Usually large (mean diameter: 5.5 cm) • Microscopy: Prominent glandular growth pattern and psammoma bodies mainly in duodenal SSToma	• Occasional association with MEN 1 and VHL • Ampullary/duodenal SSToma often associated with NF1	Mostly malignant, 66% present with metastasis

Adapted from [1, 3]

Abbreviations: *ECL* enterochromaffin-like, *MEN 1* multiple endocrine neoplasia type 1, *NF1* neurofibromatosis type 1, *PanNET* grade 1–3 pancreatic neuroendocrine tumor, *SSToma* somatostatinoma, *VHL* von Hippel-Lindau syndrome, *VIP* vasoactive intestinal polypeptide

PanNETs, including incidence, clinical symptoms and outcome, localization, association with inherited syndromes, and specific morphological features.

Nonfunctioning PanNETs are not associated with a distinct clinical syndrome (if sporadic). However, they may still secrete hormones, which can be detected as abnormally increased serum levels or by immunhistochemical staining of the tumor tissue. The absence of clinical symptoms can be due to hormonal release at a level that is too low to have any clinically apparent effect. Alternatively, nonfunctioning PanNETs may release hormones, such as pancreatic polypeptide (PP) or neurotensin, which do not cause symptoms. Most commonly, nonfunctioning PanNETs become clinically apparent by symptoms that are related to a large tumor size, tumor infiltration of neighboring organs, or the development of metastasis. Overall, nonfunctioning PanNETs are more common than functioning tumors and represent over 60% of all PanNETs.

The distinction between functioning and nonfunctioning PanNETs is made solely on the basis of the clinical picture. Hence, the positive result of immunhistochemical staining of the tumor tissue for a particular hormone, for example insulin, does not allow the diagnosis of an insulinoma, unless the patient presents with the corresponding clinical symptomatology. However, somatostatinomas can occasionally be an exception to this principle. The symptoms related to increased somatostatin levels are subtle and nonspecific (e.g., gallstones, diabetes, anemia, weight loss), and their connection to the PanNET may not always be appreciated clincally. In this situation, the pathologist's report on the positive immunostaining for somatostatin may sometimes prompt a reconsideration of the patient's symptomatology with subsequent correct diagnosis of a somatostinoma syndrome.

Pancreatic neuroendocrine neoplasms only rarely secrete ectopic hormones. Adrenocorticotrope hormone (ACTH)-producing pancreatic tumors account for 10% of ectopic Cushing's syndrome. Further ectopic hormones that can be secreted are growth hormone-releasing hormone and growth hormone (causing acromegaly), corticotropin-releasing hormone (Cushing's syndrome), parathyroid hormone (PTH) and PTH-related peptide (hypercalcemia), calcitonin (diarrhea), prolactin (galactorrhea, amenorrhea), and cholecystokinin (CCK).

Serotonin-producing endocrine tumors are extremely rare in the pancreas. The characteristic symptoms of the carcinoid syndrome, that is, flushing, diarrhea, and bronchoconstriction, develop only when the tumor has metastasized to the liver or retroperitoneum. Serotonin is not regarded as an 'ectopic' hormone, because low numbers of serotonin-producing extrainsular endocrine cells are present in the pancreas (see Chap. 1, Sect. 1.4.4).

Occasionally, a tumor can secrete different hormones, or the type of hormone that is expressed can change over time. The latter is usually a poor prognostic sign.

The small group of patients who develop a PanNET as part of a hereditary syndrome (MEN, VHL, NF1, TSC), may present with a complex clinical picture that is determined by the presence of other tumors and lesions associated with the genetic defect (see Sect. 20.12).

Multiple PanNETs, developing synchronously and/or metachronously raise the suspicion of a genetic syndrome but can occasionally also be seen in the absence of clinical or genetical evidence of MEN, VHL, NF1, or TSC. Recently, insulinomatosis has been described as the synchronous and metachronous occurrence of insulinomas, multiple insulinoma precursor lesions, and rare development of metastases but common recurrent hypoglycemia. This disease differs from solitary sporadic and MEN1-associated insulinomas [4].

PanNECs usually present with signs and symptoms that are similar to those of ductal adenocarcinoma of the pancreas. Most patients have metastatic disease at the time of diagnosis. Serum analysis does not usually show an elevated level of chromogranin A nor any evidence of hormonal secretion, with the occasional exception of elevated calcitonin. Unlike in PanNETs, somatostatin receptor (SSTR) scintigraphy is usually negative. PanNECs are not part of the above-mentioned genetic syndromes that may include PanNETs.

20.4 Macroscopy

PanNETs are usually well-circumscribed tumors with smooth, pushing-type contours. Some tumors may appear surrounded by a fibrous pseudocapsule (Fig. 20.1), whereas others show gross invasion into neighboring tissues and organs (Fig. 20.2). Scalloped tumor outlines raise the suspicion of gross vascular invasion (Fig. 20.3). The vast majority of PanNETs are solid tumors. While some tumors may contain cystic areas of varying size, entirely cystic PanNETs are not common and mainly present as a unilocular cavity surrounded by a rim of tumor tissue (Fig. 20.4). The tumor tissue is often a pale, red-tan, or fawn color. Black or deep yellow discoloration is rare and indicates the accumulation of lipofuscin or lipids within the tumor cells (Fig. 20.3). The tumor tissue is usually relatively soft but, depending on the extent of fibrosis or hyalinosis, PanNETs may be of a firmer consistency. Focal calcification is not uncommon.

PanNETs can vary in size from less than 1 cm to well over 5 cm (Fig. 20.5). Insulinomas are usually small (< 2 cm), probably because the associated symptomatology leads to earlier detection. Most other functioning PanNETs are of a similar size as nonfunctioning tumors, and there are no distinctive macroscopic features associated with the hormonal activity of the tumor.

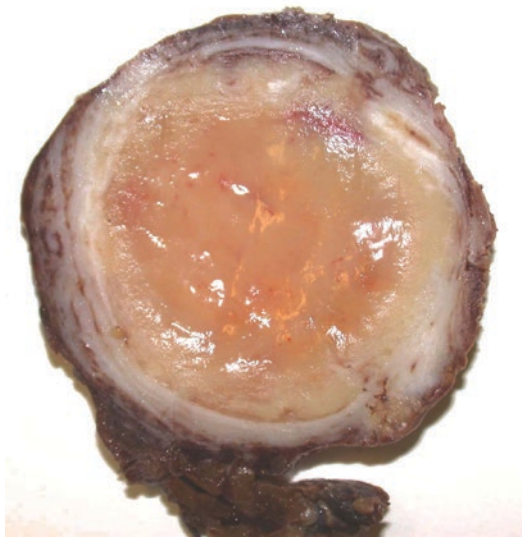


Fig. 20.1 Macroscopy of a PanNET: the tumor consists of tan-colored solid tissue with well-circumscribed pushing borders and a pseudocapsule of varying thickness

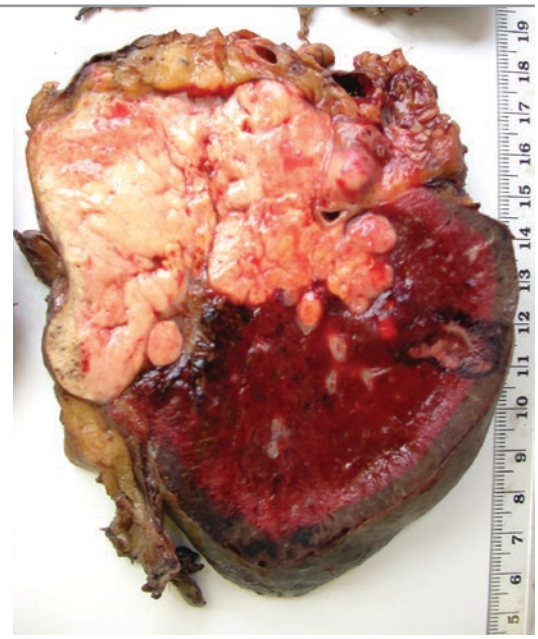


Fig. 20.2 Locally advanced PanNET: this large tumor originating from the pancreatic tail has invaded the spleen. Note the subcapsular splenic infarction

PanNETs can occur anywhere in the pancreas. A predominantly intraductal tumor location has been reported but is rare. Most sporadic tumors are single. Multiple PanNETs raise the suspicion of an underlying genetic syndrome.

In many cases, pancreatic parenchyma surrounding the PanNET shows a degree of fibrosis and atrophy. However, these changes are usually limited in extent, and pancreatic tissue further away from the tumor is often remarkably well preserved, irrespective of the tumor size. PanNETs located in the pancreatic head compress rather than infiltrate the main pancreatic duct or common bile duct. Due to the slow growth of PanNETs, adaptive dilatation of these ducts ensures proper drainage of bile and pancreatic juice (see Fig. 19.16).

PanNECs are usually large at the time of diagnosis. They consist of fleshy, grey-white tissue that may be better delineated than ductal adenocarcinoma (Fig. 20.6). Necrosis and hemorrhage of varying extent may be visible.

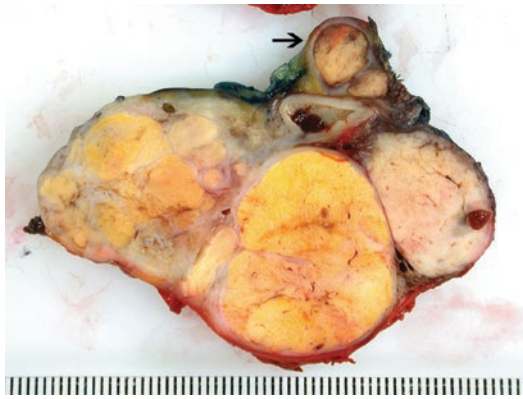


Fig. 20.3 Gross vascular invasion in a PanNET: the tumor has a multinodular appearance with scalloped outlines. One of the tumor nodules represents gross invasion of the splenic vein (*arrow*). Note the bright *yellow* color of part of the tumor as a result of the accumulation of lipids within the tumor cells (same tumor as in Fig. 20.8)

20.5 Microscopy

Neuroendocrine tumors of the pancreas can exhibit a wide variety of microscopic appearances but, with few exceptions, these are of no known clinical or prognostic relevance. The main significance of the morphological variation in growth pattern and cytomorphology lies in the awareness of its existence and the distinction from other tumor entities.

In this section, the microscopic features of PanNETs grade 1–3 and PanNECs will be described, while a more detailed discussion of the WHO classification 2019 follows separately (see Sect. 20.6).

20.5.1 Pancreatic Neuroendocrine Tumors (Grade 1–3)

PanNETs grade 1–3, as defined by the WHO classification 2019, constitute a group of well-differentiated endocrine tumors (see Table 20.1). They represent the vast majority of all endocrine neoplasms in the pancreas. Their diagnostic hallmarks are cytological uniformity and a so-called organoid growth pattern. A wide range of such growth patterns exists (Fig. 20.7): trabecular, ribbon-like, acinar, glandular, cribriform, pseudorosette-like, gyriform, insular, nested, and

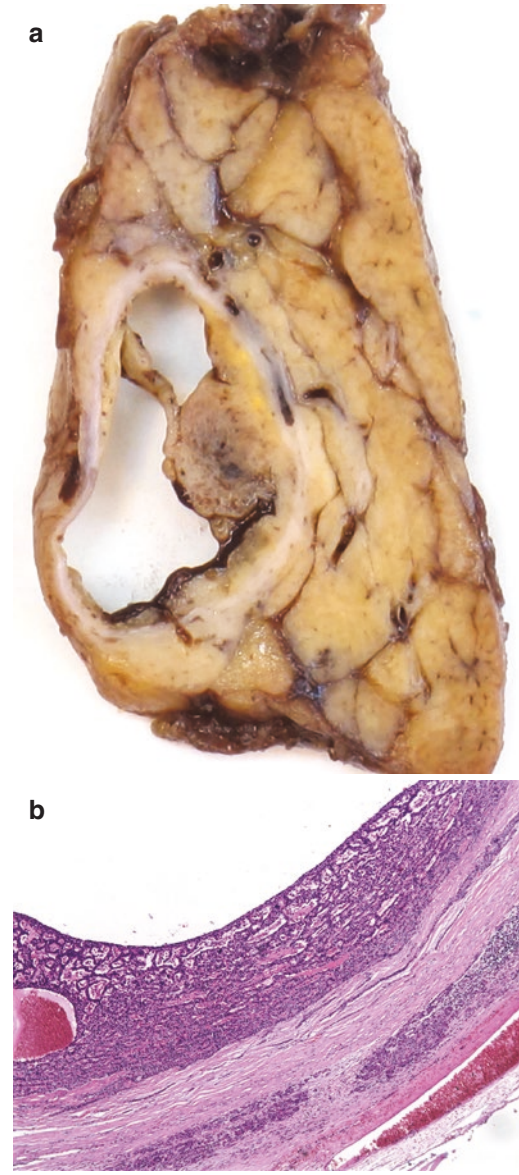


Fig. 20.4 Cystic PanNET: the tumor consists of a single cystic cavity surrounded by a rim of tumor tissue (**a**). The latter shows microscopic features characteristic of a PanNET (**b**). In this case, the focal presence of more extensive tumor tissue within the cystic PanNET was misinterpreted on preoperative imaging as a mural nodule in a mucinous cystic neoplasm

occasionally solid. In PanNETs with an angiomatoid pattern, small lakes of erythrocytes are present within dilated glandular tumor cell structures and occasionally also in the intervening stroma. It is not uncommon to find several different growth patterns within a single tumor.

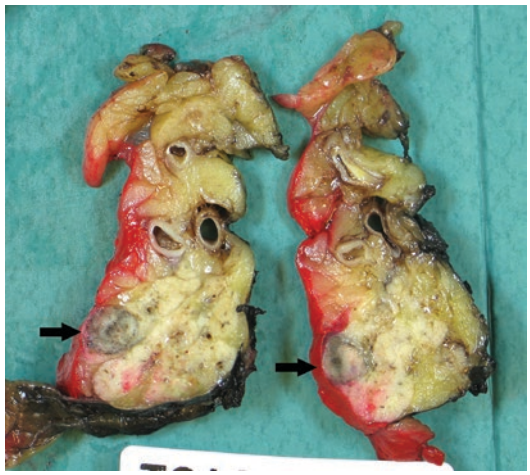


Fig. 20.5 Incidental PanNET: this 0.9 cm large tumor (*arrows*) was found incidentally in a distal pancreatectomy specimen resected for intraductal papillary mucinous neoplasia (not shown)

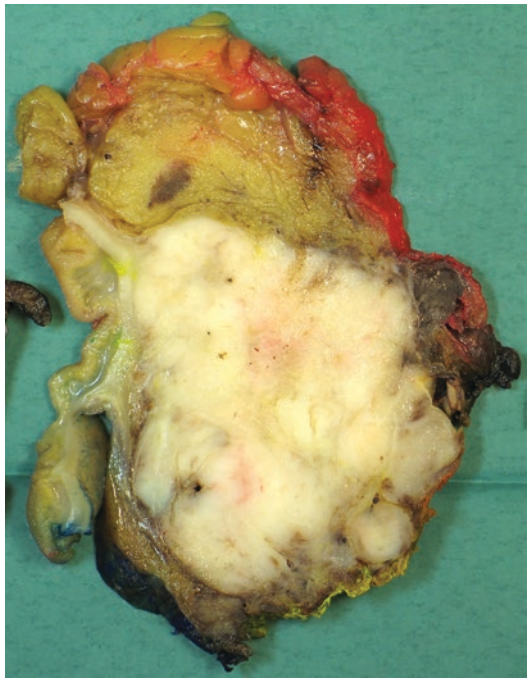


Fig. 20.6 Macroscopy of a PanNEC: the tumor consists of fleshy, grey-white tissue with well-circumscribed, scalloped outlines

Cytologically, PanNETs usually exhibit only a mild degree of pleomorphism, although exceptions are well recognized (see below). The tumor cells usually contain a round to ovoid nucleus, which is located in the center of the tumor cell, but may be polarized in tumors with a trabecular growth pattern. Chromatin is predominantly coarsely stippled, resulting in a 'salt and pepper' appearance. Nucleoli are usually absent or small and present in only a proportion of the tumor cell population. Mitotic figures are rare and atypical mitotic figures exceptional. The tumor cells usually have a cuboidal or polygonal shape and contain a copious amount of finely granular, amphophilic, or eosinophilic cytoplasm. While these features characterize the majority of PanNETs, there are multiple distinct, but usually rare, variants. Not uncommonly, only a proportion of the tumor cells show features of a particular variant. There is currently no agreed cut-off value, but in general it is suggested that a 'significant' proportion of the tumor cell population—set by some arbitrarily at 25% or more—should exhibit the specific morphology for it to be reported. As most of these variants have no known correlation with clinical features, it suffices to report on the presence of the variant morphology together with an estimate of its extent.

The *clear cell variant* of PanNETs is characterized by the presence of abundant cytoplasm with countless clear vesicles, which impart a foamy appearance, similar to that of sebaceous cells (Fig. 20.8), and may scallop the nuclei. As the cytoplasmic vacuoles contain lipid, the term *lipid-rich variant* is also used. This variant is more common in patients with von Hippel-Lindau syndrome, who are at risk of developing—amongst various other lesions—renal cell carcinoma, which has a known propensity to metastasize to the pancreas. The differential diagnosis of clear cell variant PanNET and metastatic renal cell carcinoma of clear cell type is discussed in Chap. 12, Sect. 12.5.

In the *oncocytic variant*, the tumor cells also contain abundant cytoplasm, but this is granular and eosinophilic in appearance due to the accumulation of mitochondria. Tumor cells of this variant often show moderate nuclear atypia with more than usual nucleolar prominence (Fig. 20.9). Oncocytic nonfunctioning PanNETs seem to be more aggressive.

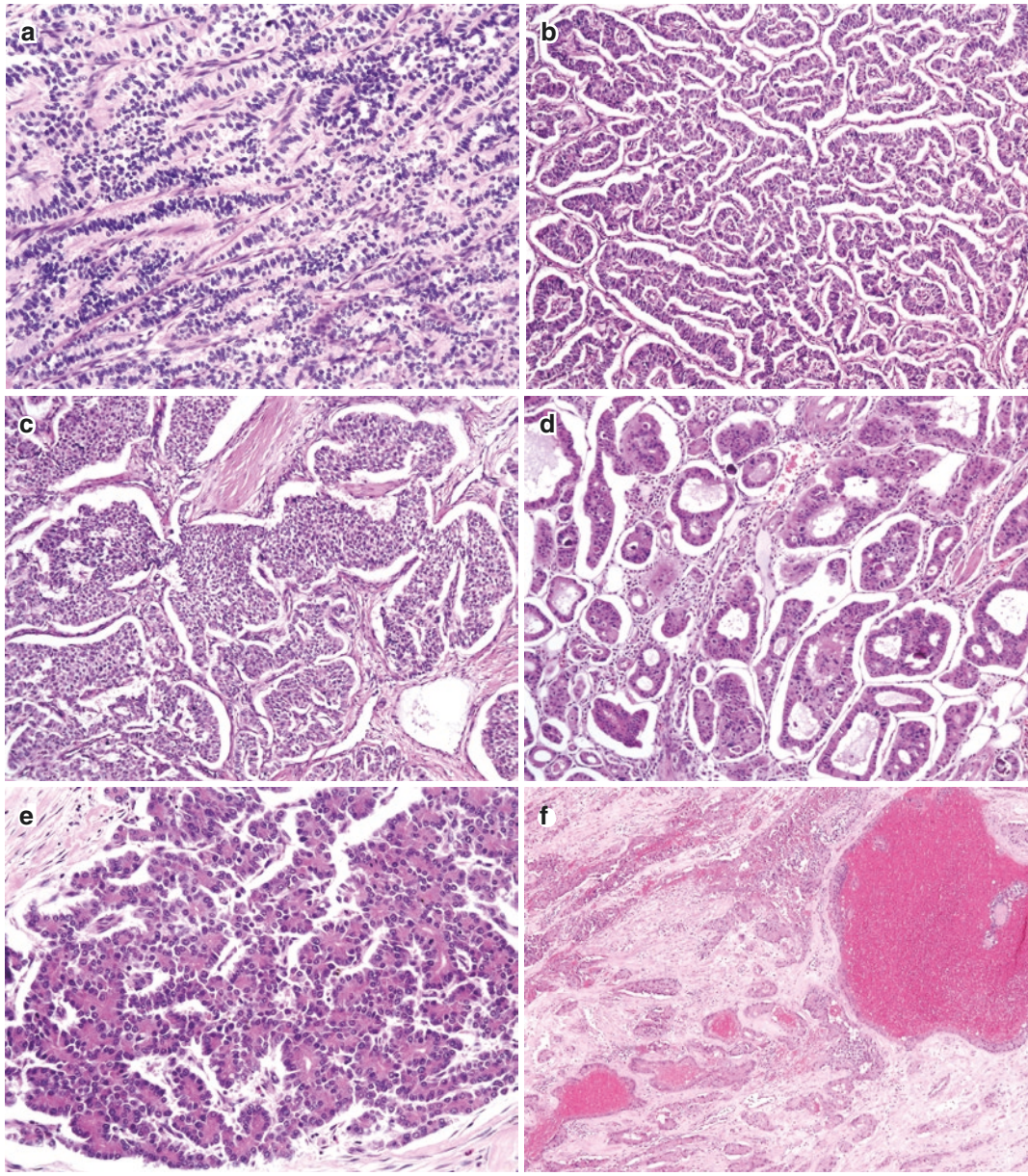


Fig. 20.7 Growth patterns of PanNETs: grade 1–3 pancreatic neuroendocrine tumors can show a range of organoid growth patterns: ribbon-like (**a**), gyriform (**b**), insular (**c**), glandular (**d**), acinar (**e**), and angiomatoid (**f**)

In the *pleomorphic variant*, the tumor cells display moderate to marked nuclear atypia (Fig. 20.10). However, this is not associated with increased proliferative activity or necrosis, and the tumor cells with large nuclei usually also have copious cytoplasm ('cytomegaly'), that is, the nucleus:cytoplasm ratio remains unaltered. These features are helpful in distinguishing the pleomorphic PanNET variant from other high-grade malignant neoplasms, such as adenocarcinoma or PanNEC. There is no convincing evidence that pleomorphic PanNETs are more aggressive in their behavior than conventional PanNETs.

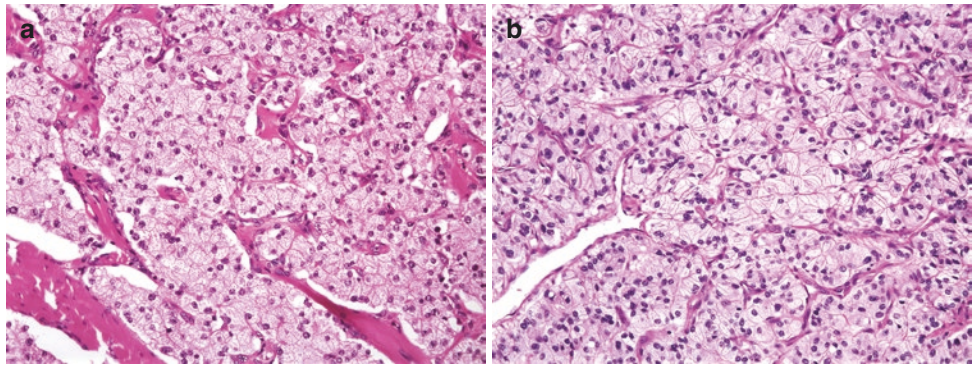


Fig. 20.8 Clear cell or lipid-rich PanNET: the tumor cells have a clear cytoplasm, which contains more (**a**) or less (**b**) conspicuous microvesicles. The tumor in (**b**) is the same as in Fig. 20.3 and stems from a patient with von Hippel-Lindau syndrome

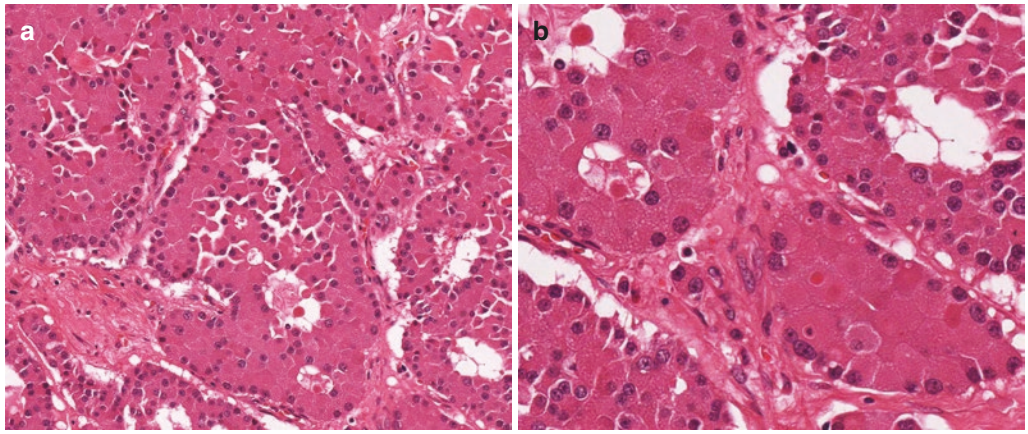


Fig. 20.9 Oncocytic PanNET: tumor cells have copious, deeply eosinophilic, and granular cytoplasm (**a**). There is mild nuclear pleomorphism, and multiple tumor cells have one or two nucleoli (**b**)

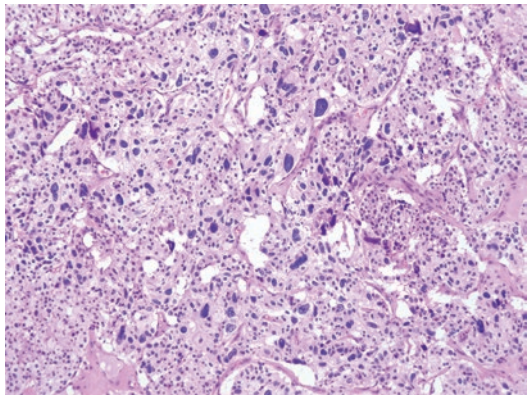
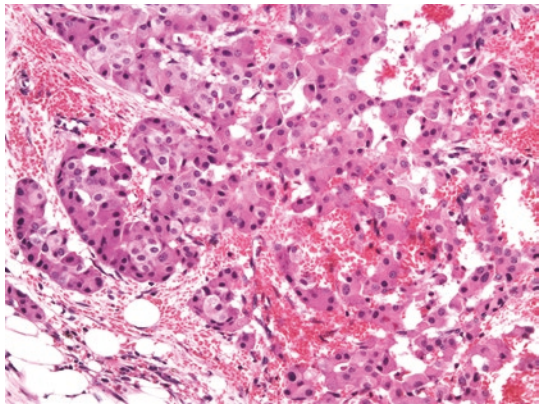


Fig. 20.10 Pleomorphic PanNET: there is marked nuclear pleomorphism. Note the absence of mitotic figures and the abundance of cytoplasm in cells with large hyperchromatic nuclei ('cytomegaly')

The so-called *rhabdoid variant* is characterized by prominent, hyaline, pale, or eosinophilic intracytoplasmic inclusions. The term 'rhabdoid' is in fact a misnomer, because the cellular inclusions are composed of keratin whorls.

In the *hepatoid variant*, the tumor cells resemble hepatocytes because of the glycogen-containing cytoplasm, the vesicular nucleus with a prominent nucleolus, and the positive immunolabeling for hepatocellular markers (at least HepPar1). These tumors show a perisinusoidal growth pattern, can contain bile canaliculi, and may occasionally contain bile droplets (Fig. 20.11). This rare variant is of clinical relevance, because it is associated with prominent



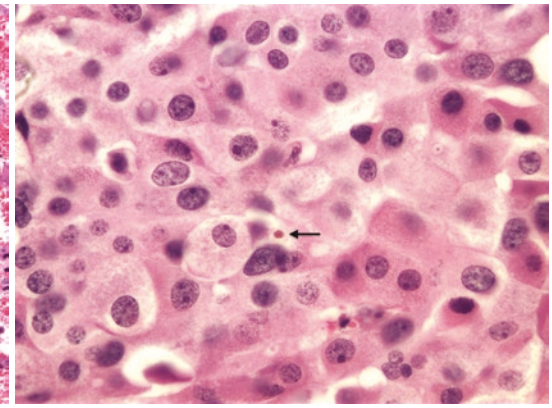


Fig. 20.11 Hepatoid PanNET: tumor cells with ample eosinophilic cytoplasm and a central round nucleus resemble hepatocytes. Note the liver-like trabecular arrangement and sinusoidal vascular network (**a**) as well as the presence of a bile droplet (**b**; *arrow*) (Reproduced with permission from Verbeke [5]. Blackwell Publishing Ltd)

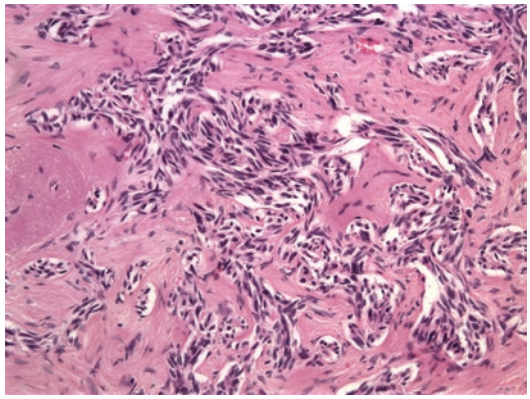


Fig. 20.12 Spindle cell variant of PanNET: endocrine tumor cells are spindle shaped and arranged in short irregularly intersecting bundles. Note the cytological uniformity of the tumor cells (Reproduced with permission from Verbeke [5], Blackwell Publishing Ltd)

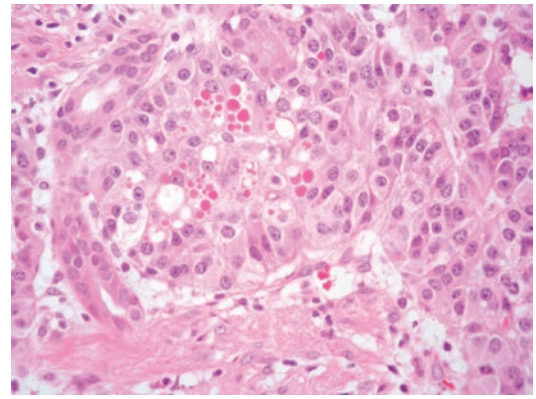


Fig. 20.13 PanNET with globules: eosinophilic round globules of varying size are present within the cytoplasm of tumor cells and occasionally also in the extracellular space

vascular invasion, early liver metastasis, and a shorter survival. As similar hepatoid features may be seen in ductal adenocarcinoma of the pancreas (see Chap. 9, Sect. 9.14.5), this should always be considered as a differential diagnosis.

Spindle cell morphology is a rare and often focal feature (Fig. 20.12).

Tumor cells may contain PAS-positive *globules*, which can also be present extracellularly (Fig. 20.13). Psammoma bodies are most frequently seen in somatostatinomas (Fig. 20.14) and can also be found in insulinoma. Rare cases of a *pigmented variant* have been reported, in

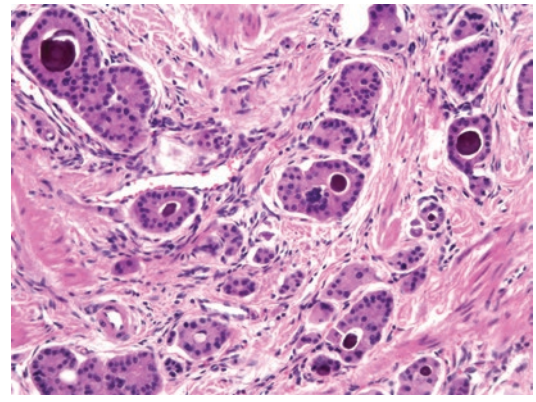


Fig. 20.14 PanNET with psammoma bodies: round and deeply basophilic psammoma bodies are present within the glandular lumina of a somatostatinoma

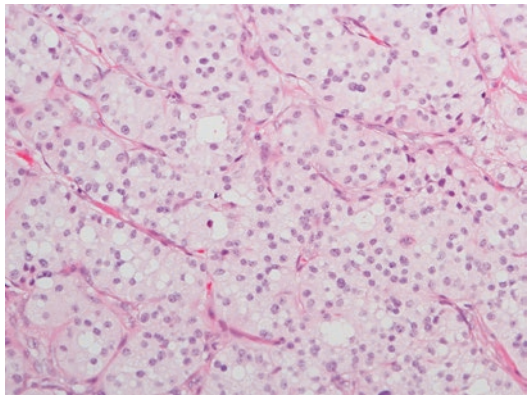


Fig. 20.15 Stroma in PanNET: a delicate fibrovascular network supports the tumor cell nests

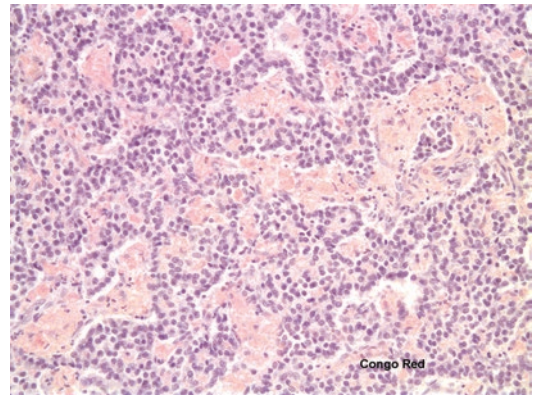


Fig. 20.17 Insulinoma with amyloid: Congo red staining highlights the amorphous intercellular deposits of amyloid in an insulinoma

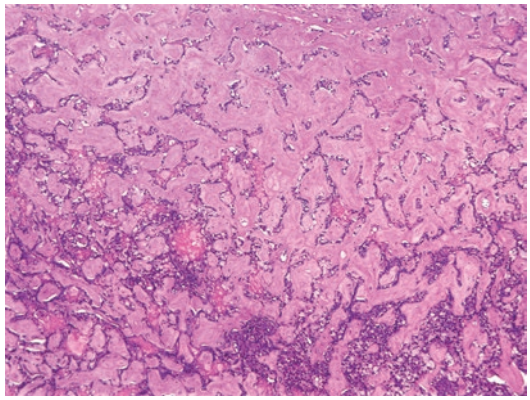


Fig. 20.16 PanNET with hyaline stroma: tumor cell trabeculae are small and widely spread in this prominent hyaline stroma

which the dark brown-black color, visible both macroscopically and microscopically, is due to the accumulation of lipofuscin.

The stroma in PanNETs characteristically consists of a delicate fibrovascular network (Fig. 20.15). However, a hyaline stroma is not uncommon and is seen more frequently in insulinoma than in other PanNETs. On occasion, the hyaline stroma may be prominent and nearly eclipse the tumor cell population (Fig. 20.16). Calcification can vary in extent and is usually irregular in shape. It does not have the stellate or egg shell configuration as seen in other pancreatic tumors (see Chaps. 15 and 16). Amyloid deposition is suggestive of an insulinoma (Fig. 20.17).

Occasionally, residual small nonneoplastic ducts and islets may be entrapped in the neoplastic proliferation, a finding that should not be misinterpreted as evidence of a nonendocrine tumor component.

20.5.2 Pancreatic Neuroendocrine Carcinomas

PanNECs are very rare in the pancreas and must be distinguished from NECs that develop somewhat more frequently in the ampulla (see Sect. 20.9.3). PanNECs are characterized by brisk mitotic activity, and they often contain areas of necrosis. Two types of PanNECs are distinguished, a small cell and a large cell type. *Small cell-type* PanNEC resembles small cell carcinoma in other sites. It is characterized by diffuse sheets of small to medium-sized cells with minimal ill-defined cytoplasm. The tumor cell nuclei have a finely granular chromatin, do not usually contain nucleoli, and may show nuclear molding (Fig. 20.18). Within the group of PanNECs, the small cell type is less common compared with the large cell type. Small cell-type PanNECs tend to be larger in size and have a higher proliferative index than the PanNECs of large cell type [6].

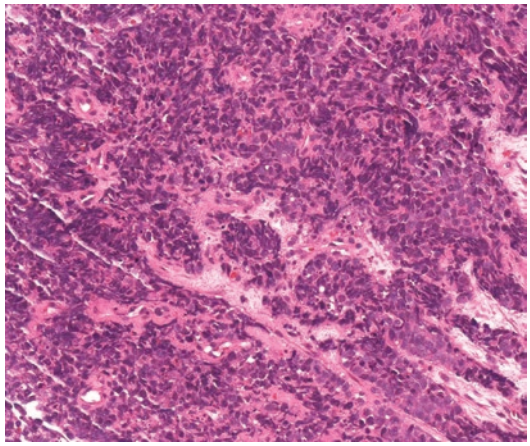


Fig. 20.18 PanNEC of small cell type: small to medium-sized tumor cells with minimal ill-defined cytoplasm grow in indistinct solid sheets. The tumor nuclei show a diffuse chromatin pattern without nucleoli

Large cell-type PanNEC is composed of large round to polygonal cells with a moderate amount of cytoplasm. The nuclei are large and show coarsely clumped chromatin and often a prominent nucleolus (Fig. 20.19). In most cases, mitotic activity is not as high as in the small cell type but remains usually well above 20 mitotic figures/10 high power fields, as defined by the WHO classification 2019 (see Sect. 20.6). Some of the tumors may show a more or less organoid rather than an indistinct solid growth pattern. Large cell-type PanNECs are more common and account for approximately 60% of the PanNECs.

The distinction between small and large cell type is important first and foremost for diagnostic purposes. Awareness of both cell types will avoid misdiagnosis of other poorly differentiated tumors, in particular poorly differentiated adenocarcinoma in the case of large cell-type PanNEC, and neoplasms from the group of 'small blue round cell tumors' in the case of small cell-type PanNEC (see Sect. 20.9.2). Whether the different cell types are associated with differences in tumor behavior, response to chemotherapeutic treatment, and patient outcome has not yet been well established. However, recent data indicate that both types are at least genetically similar and clearly distinct from grade 1–3 PanNETs [6].

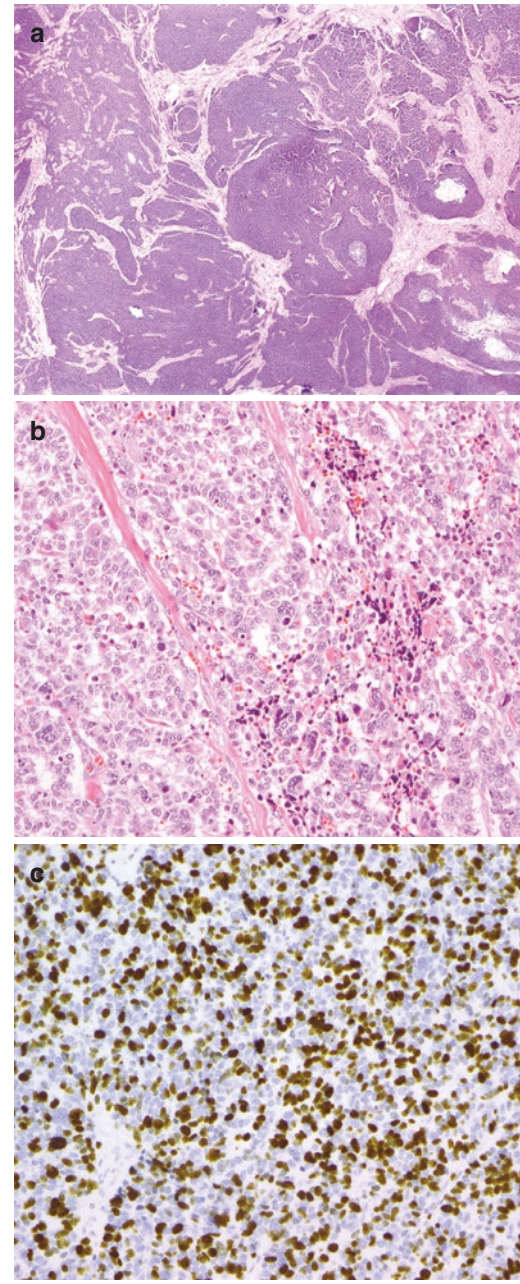


Fig. 20.19 PanNEC of large cell type: solid tumor sheets and clusters of varying size (**a**) are composed of large tumor cells with pleomorphic vesicular nuclei. Note the presence of foci of tumor cell necrosis (**b**). Immunostaining for Ki67 shows high proliferative activity (Ki67 index: 62%) (**c**)

As PanNECs lack the distinctive morphological features of their grade 1–3 counterparts, immunohistochemistry for neuroendocrine markers is usually required to reach a definitive diagnosis (see Sect. 20.7.1).

20.6 Classification

The WHO classification 2019 introduced the entity PanNET grade 3 in recognition of the existence of neuroendocrine tumors that morphologically, clinically, and genetically are similar to PanNET grade 1–2 but show a proliferative activity that exceeds 20% (Ki67 proliferative index) or >20 mitotic figures/10 high-power fields (HPF) (Fig. 20.20).

The classification of pancreatic neuroendocrine neoplasms is based on *morphology* and proliferative activity. As described above, PanNETs (grade 1–3) show a relatively monotonous microscopic morphology with mild nuclear atypia and a variety of organoid growth patterns that are characteristic of these tumors. Tumor necrosis is not usually seen. In contrast, PanNECs usually lack a convincing organoid tumor growth pattern, often contain multifocal necrosis, and may show marked cytological atypia.

The *proliferative activity* in PanNETs grade 1–3 and PanNECs is summarized in Table 20.3. Either the Ki67 index or the mitotic count, or both, can be used to assess the proliferative activity. In PanNECs, the Ki67 index usually well exceeds the threshold of 20%: in the vast majority of cases it is >50%, and it commonly ranges between 60 and 80%. However, lower proliferative activity, between 20 and 50%, may be seen, especially following chemotherapy. Conversely, PanNETs grade 3 usually show a lower Ki67 index than that seen in PanNECs, but values as high as 70–80% have been reported. Consequently, proliferative activity cannot be used as the sole criterion to distinguish between PanNET grade 3 and PanNEC.

In general, the Ki67 index is preferable to the mitotic rate, in particular when reporting on a small tumor sample, for example, a biopsy of the primary pancreatic tumor or a liver metastasis, because Ki67-positive cells are usually more numerous than mitotic figures. Practical issues regarding the evaluation of the Ki67 index are discussed below. Screening for mitoses should be performed on at

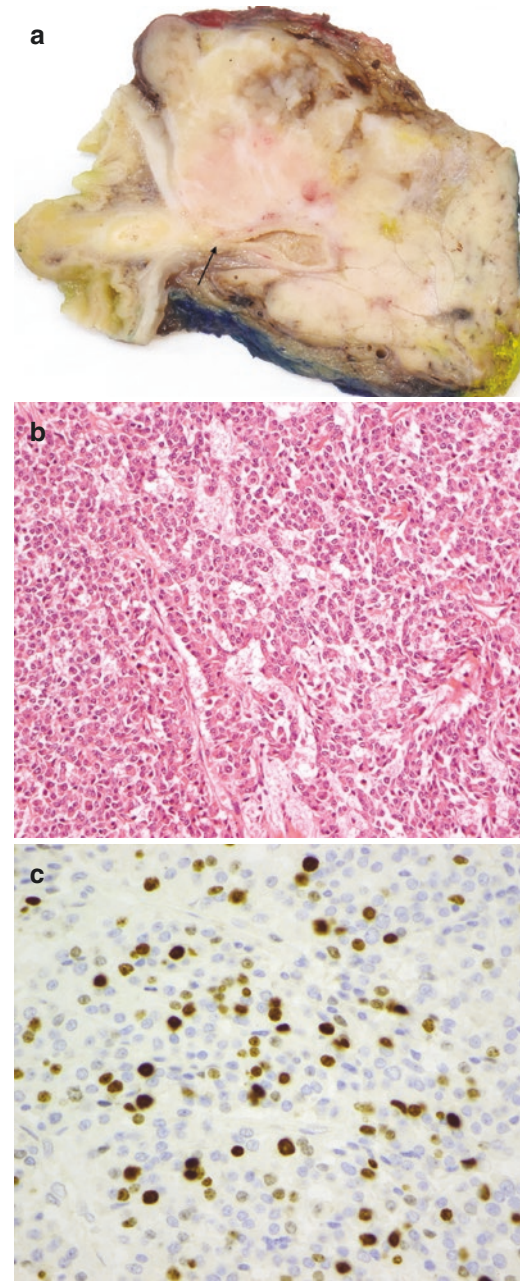


Fig. 20.20 PanNET grade 3: a fairly poorly demarcated tumor consisting of pale, soft tissue compresses the junction of the main pancreatic duct with the ampulla of Vater (*arrow*), resulting in dilatation of the former (**a**). Histologically, the tumor shows features of a well-differentiated neuroendocrine tumor (**b**), but the Ki67 index is 40% (**c**: immunostaining for Ki67)

Table 20.3 Grading of pancreatic neuroendocrine neoplasms according to the WHO classification 2019 [1]

Terminology	Differentiation	Grade	Mitotic count	Ki67 index
PanNET, G1	Well differentiated	Low	<2/10 HPF	<3%
PanNET, G2		Intermediate	2–20/10 HPF	3–20%
PanNET, G3		High	>20/10 HPF	>20%
PanNEC, small-cell type PanNEC, large-cell type	Poorly differentiated	High	>20/10 HPF	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Abbreviations: *G* grade, *HPF* high power fields, *MiNEN* mixed neuroendocrine—non-neuroendocrine neoplasm, *PanNEC* pancreatic neuroendocrine carcinoma, *PanNET* pancreatic neuroendocrine tumor

least 50 fields of 0.2 mm^2, an area that equals 10 HPF at 400x magnification (and an ocular field diameter of 0.5 mm). In case of discrepant findings between Ki67 index and mitotic count, the tumor should be graded according to the higher proliferation rate. In most such cases, the Ki67 index is found to be higher than the mitotic count.

As future changes to the cut-off values of either the mitotic count or the Ki67 index may occur, it is important to record the exact value for either parameters, to allow regrading of tumors following future amendments to the grading system [7, 8].

Because PanNETs and PanNECs differ genetically [6], immunohistochemistry may help, in particular with distinguishing PanNEC from PanNET grade 3. As PanNECs usually harbor mutant *TP53* and inactivation of the RB1/p16 pathway, they are characterized by immunopositivity for TP53 and loss of staining for RB1 or p16.

20.7 Immunohistochemistry

Immunohistochemistry is an integral part of the diagnostic work-up of pancreatic neuroendocrine neoplasms. The indications for immunostaining and the use of various markers are discussed below.

20.7.1 Confirmation of Neuroendocrine Differentiation

All suspected pancreatic endocrine neoplasms should be immunostained with the generic neuroendocrine markers synaptophysin and chromogranin A. While immunopositivity for the former is usually strong and diffuse, chromogranin immunopositivity can be more focal or even negative in poorly granulated, that is, less well differentiated tumors. Therefore, the rare PanNECs arising in the pancreas are often only faintly and focally immunopositive for chromogranin, especially the small cell type, in which tumor cells have only scant cytoplasm with few neurosecretory granules. Although immunohistochemistry for neuroendocrine markers is particularly important to establish the diagnosis of a PanNEC and exclude other differential diagnoses, there are currently no recommendations as to the intensity and extent of labeling that is required to confirm the diagnosis. It should be borne in mind that expression of neuroendocrine markers—usually only focally—may also be found in non-endocrine neoplasia, in particular acinar cell carcinoma (see Sect. 20.9.1). If the amount of tissue is limited (e.g., in biopsy material), synaptophysin is the best single neuroendocrine marker to use. Neuron-specific enolase (NSE), PGP9, CD56, and CD57 are not recommended, as these markers are of limited specificity. Similarly, histochemical stains such as the Grimelius silver stain are nonspecific, and their use is therefore no longer recommended. Other immunohistochemical markers that may be helpful in the distinction of pancreatic neuroendocrine neoplasia from other pancreatic tumors are discussed in the section on differential diagnosis. On rare occasion, a diagnosis of small-cell PanNEC may be reached in the absence of positive immunostaining for synaptophysin and chromogranin A, based on morphology, Ki67 index/mitotic count, and careful exclusion of other differential diagnoses [9].

20.7.2 Evaluation of Hormonal Production

Immunohistochemical evaluation of hormonal production is generally not required for the diagnosis of every pancreatic neuroendocrine neoplasm, as the diagnosis of a functioning neuroendocrine tumor is determined by the presence of a clinical syndrome due to hormonal oversecretion, irrespective of immunohistochemical findings. However, as an exception to the rule, a PanNET that is immunopositive for pancreatic polypeptide (PP) can be diagnosed as a 'PPoma', since overproduction of this hormone remains clinically silent. For all other hormones, positive immunolabeling in the absence of the corresponding clinical symptoms does not justify the diagnosis of a functioning tumor. Instead, the tumor may be reported as, for example, a grade 1 PanNET with immunohistochemical evidence of glucagon production.

While immunohistochemistry for hormones is generally not needed, there are three scenarios in which it is required. First, in patients with a clinical syndrome due to hormonal oversecretion, immunohistochemical confirmation that the surgically resected tumor is indeed the source of hormone overproduction is considered good practice. However, it should be borne in mind that the immunohistochemical findings in the tumor tissue may not always correlate with the biochemical or clinical evidence of hormone production. Immunolabeling may be absent in functioning tumors if the hormone is quickly released from the tumor cells and intracytoplasmic hormone levels remain undetectably low. Conversely, immunostaining may be positive for a particular hormone without corresponding clinical syndrome or even serum levels, as the tumor may produce but not release the hormone, or the hormone may be secreted at levels too low to cause clinical symptoms.

Second, positive immunostaining for somatostatin in a resected PanNET may sometimes prompt the (retrospective) clinical identification of a somatostatinoma syndrome, whose symptoms can be subtle and nonspecific (see Sect. 20.3). Morphological findings that may raise the suspicion of somatostatinoma are psammoma bodies and a glandular growth pattern, especially if the patient has neurofibromatosis 1 and the tumor is located in the ampulla or duodenum.

A third indication for immunohistochemical hormone detection is the confirmation of the neoplastic nature of a small endocrine cell lesion. Occasionally, it may be difficult to confidently distinguish small PanNETs or endocrine microadenomas (see Sect. 20.15) from enlarged islets of Langerhans, for example, in the context of chronic pancreatitis. Immunohistochemical demonstration of the preservation or loss of the numerical and specific spatial distribution of the various hormone-producing cells (positive for insulin, glucagon, somatostatin, and PP) will indicate the correct diagnosis (see Fig. 20.35). While endocrine microadenomas usually immunostain diffusely for a single hormone (most commonly glucagon, followed by PP), up to 40% of nonfunctioning PanNETs may show positive immunostaining for multiple hormones, most frequently glucagon, followed by PP and somatostatin.

20.7.3 Ki67 Immunostaining

Immunostaining for Ki67 should be performed on every pancreatic neuroendocrine neoplasm, because the proliferative activity is a defining criterion of tumor grade. As proliferative activity may vary within the same tumor, the proliferation index, that is, the percentage of tumor cells showing nuclear Ki67 immunolabeling, should be assessed in the areas of highest labeling, the so-called hot spots. Recommendations vary regarding the number of tumor cells that are to be counted. The WHO classification 2019 suggests that 500 tumor cells should be counted [1], whereas the European Neuroendocrine Tumor Society (ENETS) proposes assessment of 500–2000 tumor cells in hot spots [10]. Eye-piece grids may be helpful when counting. An alternative, relatively simple, and reliable approach is to take one or several high-power microphotographs from the hot spots and to count the positive and negative tumor cells, either on a paper print of the

microphotograph or directly on screen using image processing software. It is currently not known if the proliferation index should be assessed in multiple disease sites, that is, the primary tumor and lymph node or liver metastasis.

Assessment of the proliferative activity by counting mitoses is usually a less desirable option, because identification of the hot spots is more difficult for mitotic figures than for Ki67-positive cells.

20.7.4 Other Prognostic Factors

Several factors, including expression of CK19 and CD117, or loss of expression of CD99, progesterone receptor, or PTEN have been reported to allow prognostic substratification of PanNETs. However, validation of these factors is still awaited and therefore their use is currently not recommended.

20.7.5 Biopsy Diagnosis of Liver Metastasis

Because over 50% of patients with pancreatic endocrine neoplasia present with liver metastasis at the time of diagnosis, liver biopsy specimens from such metastatic tumor deposits are not uncommon. Reporting on these samples requires first and foremost the immunohistochemical confirmation of the neuroendocrine nature of the tumor. The grade of tumor differentiation should be determined as discussed above, that is, a formal assessment of the Ki67 index should be performed, as this has important management implications. Evaluation of the proliferative activity in biopsies is obviously limited by the small sample size.

Immunostaining for ISL1 (insulin gene enhancer protein) provides the best support for confirming the pancreatic origin of a metastatic neuroendocrine tumor deposit, but it should be kept in mind that up to 20% of liver metastases of PanNETs may be negative [11]. Of some, but less reliable, help are PDX1 (which is also positive in duodenal NETs), CDX2 (which is mainly, but not exclusively a marker of midgut NETs), and PAX8 (which is positive in approximately 50% of metastatic PanNETs) [12, 13]. TTF1 is present in over 60% of well-differentiated neuroendocrine tumors of pulmonary origin, but cannot be used for NECs, because the latter may also be positive even if of extrapulmonary origin. Cytokeratin staining (CK7, 19, 20) is unhelpful, because—unlike adenocarcinomas—the cytokeratin expression profile in neuroendocrine tumors does not directly relate to the tissue of origin. A proportion of PanNETs may stain positively for CK7, as do the majority of bronchopulmonary and a small number of gastrointestinal neuroendocrine tumors. Absence of immunolabeling for serotonin may be a further useful test, as serotonin-producing tumors are mainly of intestinal origin and exceedingly rare in the pancreas [11]. Conversely, positive immunostaining for insulin or glucagon is indicative of, but not specific for, a pancreatic origin. It should be borne in mind that metastases may occasionally produce hormones that differ from those found in the primary tumor.

20.8 Staging

20.8.1 Primary Tumor

Staging of PanNETs is done according to the UICC TNM (eighth edition) for these tumors [14] (Table 20.4). The staging criteria are tumor size, with 2 cm and 4 cm as thresholds, and the extent of the tumor, separating PanNETs that are limited to the pancreas (including the peripancreatic adipose tissue) from those that invade the duodenum, bile duct, or other adjacent organs, or breach the visceral peritoneum that overlies the anterior pancreatic surface. The staging system proposed by the European Neuroendocrine Tumor Society (ENETS) is highly similar (Table 20.4) [15].

Because PanNETs are usually well demarcated, macroscopic measurement of the tumor dimensions is straightforward. However, microscopic confirmation is advisable, especially when the maximum tumor size lies at either of the cut-

Table 20.4 Staging of pancreatic neuroendocrine tumors grade 1–3 (PanNETs) according to ENETS and TNM UICC 8th edition

Stage	ENETS	TNM UICC 8th edition
T1	Tumor confined to pancreas and size <20 mm	Tumor confined to pancreas[a] and size ≤20 mm
T2	Tumor confined to pancreas and size 20–40 mm	Tumor confined to pancreas[a] and size >20 mm and <40 mm
T3	Tumor confined to pancreas and size >40 mm or Invading duodenum or bile duct	Tumor confined to pancreas[a] and size >40 mm or Invading duodenum or bile duct
T4	Tumor invading adjacent organs or wall of large vessels (celiac axis or superior mesenteric artery)	Tumor perforates visceral peritoneum (serosa) or invades other organs or adjacent structures
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis

Adapted from [14, 15]

[a]Invasion of adjacent peripancreatic adipose tissue is accepted but invasion of adjacent organs is excluded

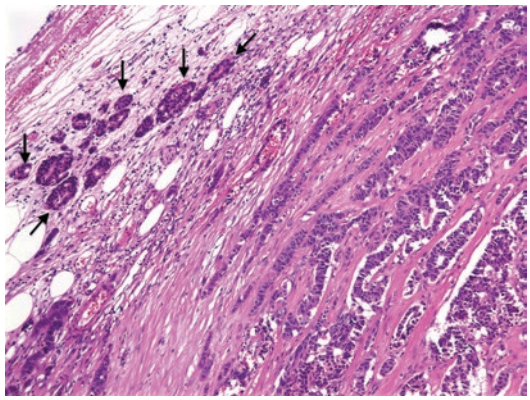


Fig. 20.21 T-staging of PanNETs: the cluster of atrophic islets (*arrows*) on the outside of the neuroendocrine tumor should not be included when measuring the tumor size

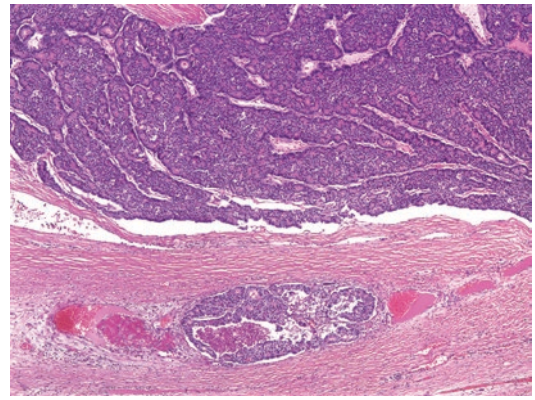


Fig. 20.22 Vascular invasion: a venous channel within the tumor pseudocapsule contains tumor cells. Note the thrombotic reaction

off points, that is, 2 cm or 4 cm. In such cases, it may be necessary to reliably distinguish between tumor cells and nonneoplastic islets at the tumor edge (Fig. 20.21). If needed, immunohistochemical staining for insulin, glucagon, somatostatin, and PP can help distinguish residual islets from tumor cell clusters.

Staging of PanNECs follows the UICC TNM system for ductal adenocarcinoma of the pancreas (see Chap. 9, Sect. 9.11) [14].

20.8.2 Tumor Propagation and Metastasis

The other staging descriptors—L, V, Pn, N, M—can be used to denote lymphovascular, perineural, or lymph node involvement and distant metastasis. Vascular invasion may be difficult to detect in PanNETs due to the intimate association of tumor cells with small blood vessels. Care should be taken not to misinterpret retraction artefact around tumor cell clusters as invasion of small vascular spaces. Vascular propagation is often more easily detected at the tumor periphery, where vessels may be of a larger caliber and association with the tumor may not be so close (Fig. 20.22).

20.8.3 Resection Margins

There is currently no clear definition of microscopic margin involvement (pR1), as the minimum clearance for pancreatic neuroendocrine neoplasms has not been established. However, because the majority of PanNETs are relatively well-circumscribed and

grow in a compact fashion with expansile, pushing-type margins, it has been suggested that resection can be regarded as complete, even if the margin is very close (i.e., less than 1 mm). In the absence of an evidence-based prognostically relevant definition of microscopic margin involvement, reporting of the exact distance between the tumor and the closest margin provides more robust information than a rather arbitrary attribution to R0 or R1.

Opinions differ regarding the prognostic relevance of incomplete surgical resection of a PanNET. While a positive margin does not seem to be critical for long-term overall survival, microscopic margin involvement may shorten disease-free survival in nonmetastatic PanNETs [16]. Evaluation of resection margins by intraoperative frozen section examination is usually not performed for PanNETs (see Chap. 23).

The resection margin status for PanNECs is of limited clinical significance, as these are highly aggressive malignancies, which are often diagnosed at an advanced stage and require systemic treatment.

20.9 Differential Diagnosis

In view of the enormous diversity in histological appearance of pancreatic neuroendocrine neoplasms, the list of differential diagnoses is long, and in many instances, immunohistochemistry may be required to reach a confident diagnosis. Because of the divergent morphological appearance of PanNETs and PanNECs, the differential diagnoses for both tumor groups are discussed separately. A summary of the main differential diagnostic features is shown in Table 20.5.

Table 20.5 Differential diagnosis of pancreatic neuroendocrine tumors

	Pancreatic neuroendocrine tumor	Ductal adenocarcinoma	Acinar cell carcinoma	Pancreatoblastoma	Solid pseudopapillary neoplasm
Morphology					
Compact, cellular tumor	++	–	++	++	++
Lobulated architecture	+	–	++	++	+
Pseudopapillae	+	–	–	–	++
Dense tumor stroma	+	++	–	++ (often hypercellular)	–
Salt and pepper chromatin	++	–	–	–	–
Nuclear grooves	–	–	–	–	++
Nucleoli	+	++	++	++	–
Intracytoplasmic mucin	–	++	–	–	–
PAS-positive hyaline globules	+	–	–	–	++
Squamoid nests	–	–	–	++	–
Immunohistochemistry					
CK19	+	++	+	+	–
CAM5.2	++	++	++	++	Focal
Vimentin	–/+	–	+	–	++
Chromogranin/ synaptophysin	++	Focal	Focal	+	Focal (synaptophysin only)
NSE/CD56	++	–	+	+	++
Trypsin, chymotrypsin, BCL10	–	–	++	++	–
Apha-1-antitrypsin	+	–	++	++	++
CD10	+	+	–	–	++
Beta-catenin (nuclear)	–/+	–	+	+	++
PR	+	–	–	ID	+

Abbreviations: ++ usually positive, + may be positive, – usually negative, *ID* insufficient data

20.9.1 Neuroendocrine Tumors of the Pancreas (Grade 1–3)

The single most important differential diagnosis of PanNETs is *ductal adenocarcinoma* of the pancreas. This holds true both clinically—given the different prognosis and treatment of either tumors—and from a pathology point of view. PanNETs with a glandular growth pattern, as commonly seen in somatostatinomas (see Table 20.2), may be misdiagnosed as well-differentiated adenocarcinoma. Marked nuclear atypia in pleomorphic PanNETs may cause confusion with adenocarcinoma. The low proliferative activity and nuclear-to-cytoplasmic ratio as well as the lack of mucin production exclude ductal adenocarcinoma. Immunostaining for neuroendocrine markers allows unequivocal confirmation of the neuroendocrine nature of the neoplasm. Absence of immunolabeling for MUC1 also supports the diagnosis of PanNET. However, care should be taken when using PAS-staining as a means of discrimination, because PAS-positive secretions can occasionally be found in the glandular lumina of pure PanNETs (Fig. 20.23). Similarly, there can be focal immunohistochemical staining for CA19-9 or CEA, especially in tumors with a glandular or tubular growth pattern. Cytokeratin 7 expression may be present in a small proportion of PanNETs. While the presence of psammoma bodies favors a PanNET, in particular an insulinoma or somatostatinoma, the occurrence of psammoma body-like structures has also been reported in rare cases of ductal adenocarcinoma [17, 18].

Solid pseudopapillary neoplasms of the pancreas share several features with PanNETs, which may make the distinction difficult. Both tumors can affect younger patients and present macroscopically as well-circumscribed expansile solid tumors with possible cystic areas. Microscopically, the characteristic pseudopapillary growth pattern of solid pseudopapillary neoplasms may be present only focally, while the solid areas of these tumors can mimic PanNETs in terms of growth pattern, cytological uniformity, low mitotic activity, and stromal reaction (Fig. 20.24). The presence of nuclear grooves supports the diagnosis of a solid pseudopapillary neoplasm, whereas PAS-positive globules may occasionally be seen also in PanNETs. Care should be taken not to limit immunohistochemical investigation to staining for neuroendocrine markers, because solid pseudopapillary neoplasms are diffusely positive for NSE and can show patchy labeling for CD56 and synaptophysin. Positive immunolabeling for vimentin is usually helpful in excluding PanNET, as is nuclear immunoreactivity for β-catenin, although a small proportion of PanNETs (< 5%) may show a similar staining pattern. Caution should also be taken when interpreting staining for CD10 and α1-antitrypsin, since both are positive in solid pseudopapillary neoplasms as well as in a proportion of PanNETs.

Acinar cell carcinoma can mimic PanNET by its lobulated appearance, acinar growth pattern, and low stromal content within the tumor lobules (Fig. 20.25). Immunohistochemistry is usually helpful, because acinar cell carcinomas

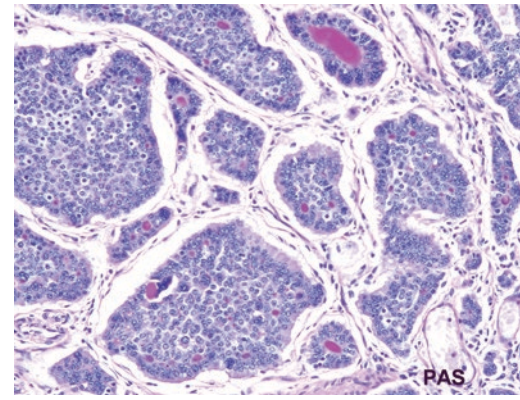


Fig. 20.23 PAS-positivity in pure PanNETs: PAS-positive secretions can occasionally be found in pure PanNETs with a glandular growth pattern. This should not be misinterpreted as evidence of exocrine differentiation

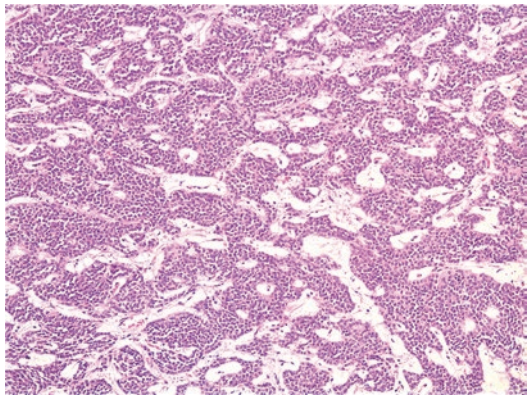


Fig. 20.24 Solid pseudopapillary neoplasm mimicking a PanNET: the organoid growth pattern, delicate stroma, and cytological uniformity in the solid area of this solid pseudopapillary neoplasm show marked resemblance to a PanNET

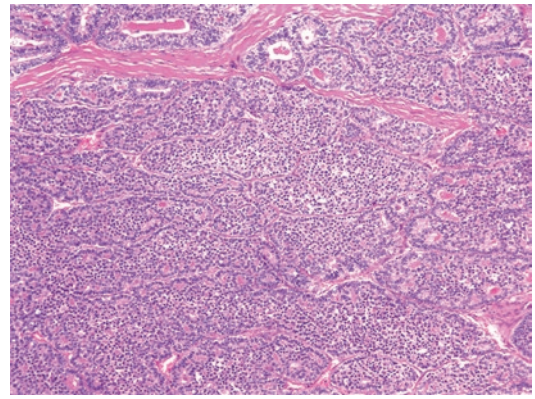


Fig. 20.25 Acinar cell carcinoma mimicking a PanNET: the acinar and insular growth pattern and low stromal component in this acinar cell carcinoma resemble a PanNET

label for (chymo-)trypsin, amylase, lipase, or BCL10. It should be borne in mind that immunostaining for chromogranin and synaptophysin can be focally positive in acinar cell carcinoma. If this is found in more than 30% of the tumor, a diagnosis of MiNEN (see Sect. 20.10) should be considered. PAS-positive granules in the apical cytoplasm also support the diagnosis of acinar cell carcinoma, but this feature is usually only present in well-differentiated tumors. Extensive necrosis is usually not a feature of PanNETs, but may occur in acinar cell carcinoma. The differential diagnosis is often more difficult if the acinar cell carcinoma is less well differentiated and characteristic features such as an acinar growth pattern or apical PAS-positivity are lacking. In that case, the nuclear morphology of the tumor cells may give a useful clue. The nuclei in acinar cell carcinoma are characterized by a vesicular chromatin pattern and a prominent central nucleolus. Moreover, the nuclei remain remarkably uniform, even if the acinar cell carcinoma has a high proliferative activity (see Chap. 10, Fig. 10.7).

Pancreatoblastoma, though rare, may also be considered. In addition to multiple histological and immunohistochemical features shared with acinar cell carcinoma, pancreatoblastoma includes squamoid nests and hypercellular stroma bands (see Chap. 10, Sect. 10.11.3).

Paraganglioma or gangliocytic paraganglioma must be excluded if a PanNET has a nested or zellballen-like growth pattern. Diffuse labeling for vimentin, absence of staining for cytokeratins, and demonstration of sustentacular cells, which stain positively for S100 and glial fibrillary acidic protein (GFAP), confirm the diagnosis of paraganglioma (Fig. 20.26). Immunohistochemical confirmation of the presence of Schwann cells and ganglion-like cells (positive for S100, GFAP, NSE and neurofilament) allows distinction of a gangliocytic paraganglioma from a PanNET (Fig. 20.27).

Metastatic renal cell carcinoma requires distinction from the clear cell variant of PanNET, especially in patients with von Hippel-Lindau syndrome, who may suffer from either or both. As renal cell carcinoma can be positive for NSE, CD56, and, on rare occasion, also for synaptophysin, vimentin is a useful marker to resolve the differential (positive in renal cell carcinoma, negative in PanNET). Further differential diagnostic criteria are discussed in Chap. 12, Sect. 12.5 and

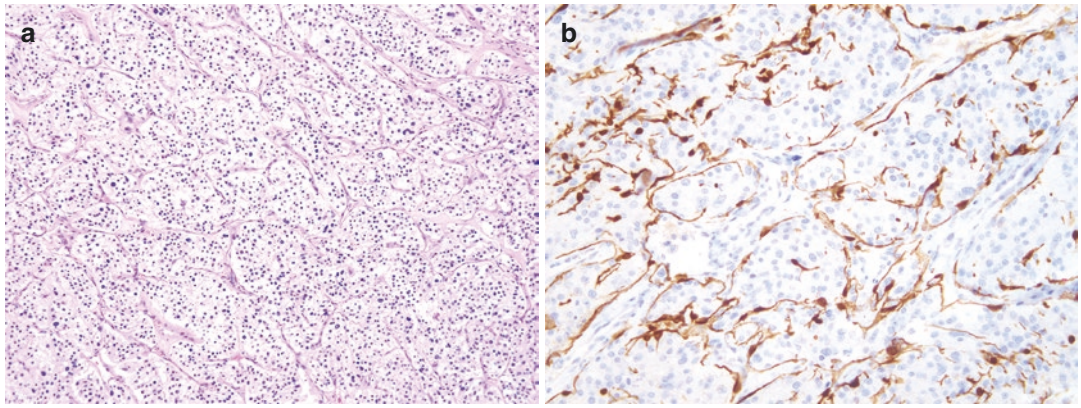


Fig. 20.26 Paraganglioma: the tumor has a 'neuroendocrine' appearance, but the zellballen arrangement (**a**) and immunohistochemical identification of S100-positive sustentacular cells (**b**) indicate that this is a paraganglioma

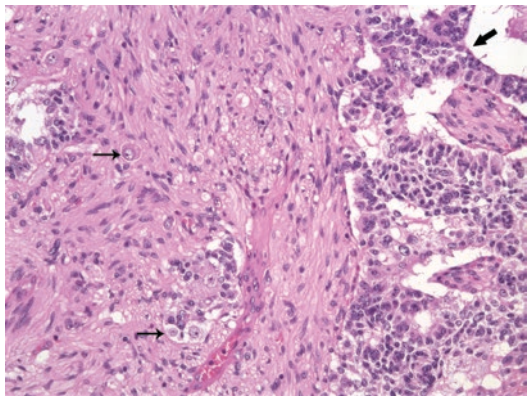


Fig. 20.27 Gangliocytic paraganglioma: this tumor is characteristically composed of three different cell populations: neuroendocrine cells (*block arrow*), ganglion-like cells (*arrows*), and spindle-shaped Schwann-like cells

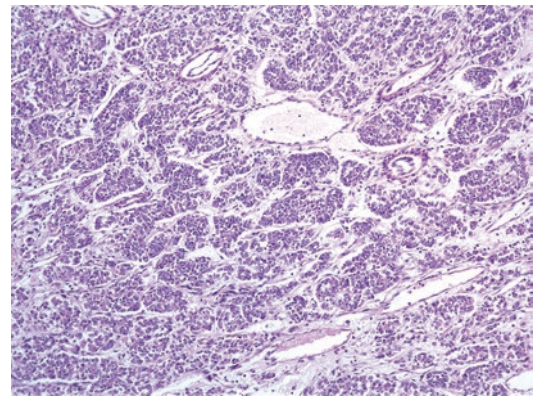


Fig. 20.28 PEComa: the nested growth pattern, cytological uniformity, and delicate fibrovascular stroma in PEComa can mimic a PanNET

summarized in Table 12.1. Oncocytic PanNET should be distinguished from *metastatic hepatocellular carcinoma* (HepPar1, arginase 1, glypican 3 positive) and *adrenal cortical carcinoma* (vimentin, melanin-A, inhibin positive; chromogranin A negative).

PEComa (perivascular epithelioid cell tumor) is a further tumor entity that can be confused with PanNET showing clear cell and spindle cell morphology (Fig. 20.28). Histological features that can be shared by both tumors are a nested growth pattern, an intimate association of tumor cells with blood vessels, a low degree of cytological pleomorphism, inconspicuous nucleoli, a possible combination of epithelioid and spindle cell morphology, and a sharp macroscopic delineation. Absence of immunostaining for generic neuroendocrine markers and positive labeling for Melan-A, HMB45, and actin and/or desmin usually allow unequivocal diagnosis of a PEComa, which very rarely can develop in the pancreas (see Chap. 11, Sect. 11.1.9).

A further differential diagnosis of clear cell variant PanNETs is the rare *solid serous adenoma* (see Chap. 15, Sect. 15.11.1).

Finally, an *ectopic adrenal cortical nodule* (see Chap. 13, Sect. 13.5, Fig. 13.8), which on rare occasion may occur in the pancreas, should not be misinterpreted as a PanNET. Immunohistochemistry may be helpful in

reaching the correct diagnosis (positive for synaptophysin; variable staining for cytokeratins; vimentin positive in some cells; absence of staining for EMA, chromogranin, S100).

20.9.2 Neuroendocrine Carcinoma of the Pancreas

The differential diagnosis of PanNECs is often challenging, as it encompasses a group of uncommon tumors, which may show only few morphological characteristics and often require specialist immunohistochemical staining and molecular testing to reach a definitive diagnosis. Because PanNECs usually have a very high proliferative activity, other tumor entities should be carefully considered if the Ki67 index is below 40%. Immunopositivity for desmin and WT1 is helpful in distinguishing PanNEC from a desmoplastic small round cell tumor (Fig. 20.29). Labeling for CD99 and Fli-1 is suggestive of a primitive neuroectodermal tumor, which can also show positive immunolabeling for neuroendocrine markers and cytokeratins (see Chap. 11, Sect. 11.1.10). High-grade malignant lymphoma may need consideration and require the use of generic leucocytic or specific lymphoma markers. Malignant melanoma may also need to be included in the differential diagnosis. Criteria to distinguish PanNEC from acinar cell carcinoma are described above. As large cell-type PanNEC may retain a certain degree of glandular or trabecular growth pattern, poorly differentiated ductal adenocarcinoma is always to be considered as a differential diagnosis. Metastatic carcinoma needs consideration and may require clinical input, as the transcription factors TTF1, ISL1, PDX1, and CDX2 may be positive in small cell carcinoma from any location.

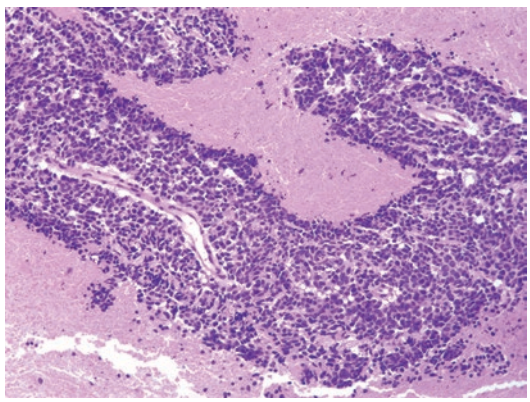


Fig. 20.29 Desmoplastic small round cell tumor: the small tumor cells with scanty cytoplasm and pleomorphic nuclei, the indistinct solid growth pattern, and the presence of necrosis resemble PanNEC

20.9.3 Neuroendocrine Neoplasms of the Ampulla, Common Bile Duct, and Duodenum

Neuroendocrine neoplasia arising from the ampulla, distal common bile duct, or duodenum is morphologically not different from primary pancreatic neuroendocrine neoplasms. As there are no known precursor lesions of these neoplasms that may aid in identifying the site of origin, the distinction is based almost exclusively on the localization of the tumor and its spatial relationship with the ampulla, distal common bile duct, or duodenal wall. However, certain neuroendocrine tumor types are more common in the ampulla and duodenum compared to the pancreas, which may help in establishing the correct diagnosis.

In the ampullary region, somatostatinoma (especially in patients with neurofibromatosis type 1), gangliocytic paraganglioma, neuroendocrine carcinoma, and mixed neuroendocrine—non-neuroendocrine neoplasm (MiNEN) are the most frequent neuroendocrine neoplasms. Gangliocytic paraganglioma and neuroendocrine carcinoma occur almost exclusively in the ampulla. Neuroendocrine neoplasms are more frequent in the major ampulla than in the minor ampulla.

The duodenum may harbor somatostatinomas, especially in patients suffering from neurofibromatosis type 1, and gastrinomas. Duodenal somatostatinomas are usually small (mean size 0.9 cm, 77% < 1 cm) compared to the larger pancreatic counterparts (mean size 3.8 cm, 6% < 1 cm). They often show a prominent glandular growth pattern and contain psammoma

bodies. Both of these features are usually absent or less prominent in pancreatic somatostatinomas. Liver metastasis at the time of presentation is rare in duodenal somatostatinoma (< 10%) but affects over half of the patients with a pancreatic primary (see Table 20.2). However, despite the small tumor size, 40–60% of the duodenal tumors have already spread to regional lymph nodes. The majority of duodenal gastrinomas occur in the clinical context of Zollinger-Ellison syndrome, either sporadically or in association with MEN1.

20.10 Mixed Neuroendocrine—Non-Neuroendocrine Neoplasm (MiNEN)

Mixed neuroendocrine—non-neuroendocrine neoplasms (MiNEN) contains two morphologically recognizable components: a neuroendocrine and a non-neuroendocrine neoplasm. Both components of a MiNEN should be characterized: ductal adenocarcinoma or acinar cell carcinoma as the non-neuroendocrine part, and PanNET or PanNEC as the neuroendocrine component (Table 20.6). MiNEN is to be distinguished from a pure pancreatic neuroendocrine neoplasm with entrapped nonneoplastic ductules. Conversely, adenocarcinoma containing scattered endocrine cells or enlarged residual nonneoplastic islets should not be mistaken for MiNEN.

MiNEN is extremely rare in the pancreas, where it represents only 0.5–2% of all ductal adenocarcinomas and 15–20% of all acinar cell carcinomas. Eighteen percent of all PanNECs are associated with an adenocarcinomatous component. Interestingly, MiNENs are less uncommon in the ampullary region, and in most of these tumors the neuroendocrine component is poorly differentiated. MiNENs are usually solid tumors that may be fairly large and show macroscopically visible areas of necrosis and cystic degeneration (Fig. 20.30).

Table 20.6 Subtypes of pancreatic mixed neuroendocrine—non-neuroendocrine neoplasms (MiNENs)

- Mixed ductal adenocarcinoma—neuroendocrine carcinoma (small-cell or large-cell)
- Mixed ductal adenocarcinoma—neuroendocrine tumor
- Mixed acinar cell carcinoma—neuroendocrine carcinoma (distinct components)
- Mixed acinar cell carcinoma—ductal adenocarcinoma-neuroendocrine carcinoma (distinct components)

Adapted from [1]

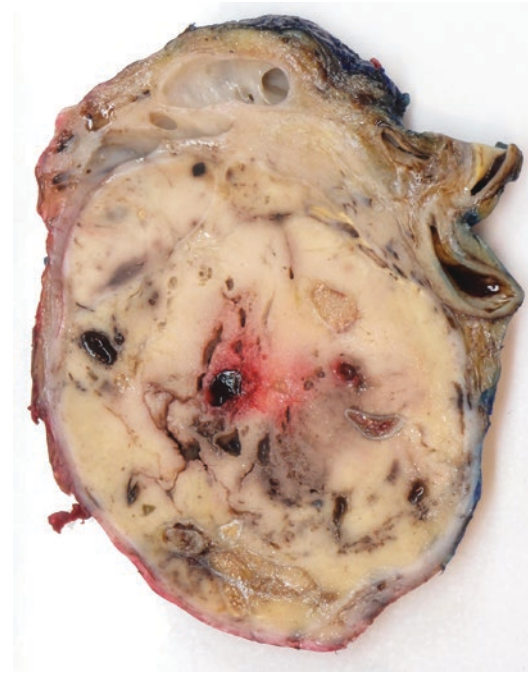


Fig. 20.30 Macroscopy of a MiNEN: this large well-circumscribed tumor in the pancreatic body consists of soft, fleshy, greyish tissue with foci of necrosis and hemorrhage. Histologically, the tumor was a MiNEN composed of NEC and acinar cell carcinoma

In pancreatic MiNENs, the neuroendocrine component is usually a NEC and only very rarely a NET (Fig. 20.31). While the outcome of a mixed ductal adenocarcinoma—PanNET is currently not known, the prognosis of a mixed ductal adenocarcinoma—PanNEC is possibly slightly better than that of a pure PanNEC. The NEC-component of a MiNEN should be characterized as small- or large-cell, and the extent of the NEC should be reported. While tumors with focal (< 30%) presence of a NEC component do not qualify as a MiNEN, the presence and extent of the NEC should be mentioned in the report.

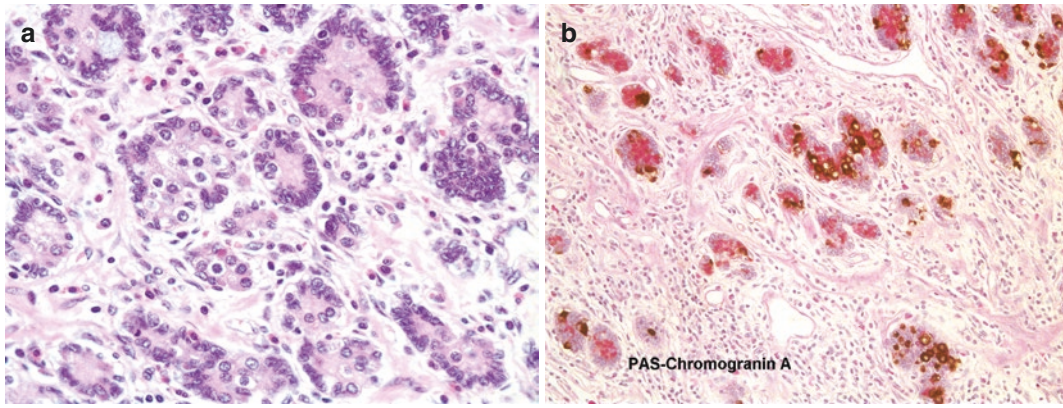


Fig. 20.31 MiNEN with a PanNET-component: the organoid growth pattern and cytological uniformity of this tumor are suggestive of a PanNET. However, scattered tumor cells have a foamy cytoplasm (**a**). PAS-staining (*pink*) combined with immunohistochemistry for chromogranin A (*brown*) reveals the intimate admixture of mucin-producing and endocrine tumor cells. Both cell populations represent >30% of the tumor (**b**)

The diagnosis of MiNENs usually requires immunohistochemical examination. Immunohistochemistry for neuroendocrine markers and Ki67 is valuable in confirming the presence of the neuroendocrine component and assessing its proliferative activity. Immunostaining for CK19 and MUC1/MUC2 can be used for confirmation of the ductal adenocarcinoma component, if the latter is poorly differentiated and cannot be unequivocally diagnosed morphologically. Interpretation of the results of PAS-staining and immunohistochemistry for CEA and CA19-9 should be circumspect, as these may also be positive in pure pancreatic neuroendocrine neoplasia, in particular in areas with a glandular growth pattern (see Sect. 20.9.1).

The definitive diagnosis of MiNENs containing acinar cell carcinoma as the non-neuroendocrine component usually requires immunohistochemical confirmation of the presence of acinar (trypsin, chymotrypsin, BCL10 positive) and neuroendocrine differentiation (synaptophysin, chromogranin positive). Both components should be present as distinct albeit closely connected compartments within the tumor. Acinar cell carcinomas in which neuroendocrine differentiation is detected only immunohistochemically do not qualify as a MiNEN (see Chap. 10, Sect. 10.8).

Mixed acinar cell carcinoma-ductal adenocarcinoma-neuroendocrine carcinoma is considered a MiNEN (Table 20.6) but it is extremely rare.

20.11 Prognosis

The prognosis for patients with PanNETs is significantly better than for those suffering from ductal adenocarcinoma. Following surgical resection, the 5-year survival rate for PanNETs (excluding insulinomas) is 65–86%, the 10-year rate 45–68%. Overall, PanNETs are more aggressive than their counterparts in the tubular digestive tract. The functional status does not convincingly influence outcome, with the exception of insulinomas, of which approximately 80–90% are benign. Patients suffering from a PanNET with ectopic hormonal production have a poorer outcome, as these tumors are usually large and have metastasized at the time of presentation.

The difference in survival between patients with local and regional disease is not significant. However, the presence of distant metastasis—usually to the liver—confers a prominent reduction in survival, the 5-year survival rate being 59% and the 10-year rate 36%. Nevertheless, many patients survive for several years following development of

liver metastasis due to the slow progression of the disease. The most important histological predictor of outcome is the proliferative activity, based on the Ki67 index or mitotic count. The newly introduced category of PanNET grade 3 progresses more rapidly than PanNET grade 2 (5-year survival rate: 29% versus 62%), but is less aggressive than PanNEC (5-year survival rate: 16%). The next most potent predictor is tumor size. Low-grade PanNETs smaller than 2 cm have a very indolent behavior, which is the rationale to suggest a watch-and-wait approach for patients with these tumors. Tumor extent, vascular invasion, necrosis, and lymph node metastasis all confer an increased risk for distant metastasis. Cystic PanNETs seem to have a better prognosis, because they often lack adverse prognostic factors and present at a lower stage. In recent years, the advancement in multimodality treatment of metastatic disease has contributed significantly to the improvement in survival. Surgery is generally the procedure of choice in patients with resectable tumors. Over 30% of patients with a PanNET have distant metastasis at the time of diagnosis, which is not necessarily a contraindication for surgical resection of the primary tumor.

PanNECs are aggressive malignancies, which often have reached an advanced and unresectable stage at the time of diagnosis. Accordingly, the prognosis is only 6–12 months. Less than 25% of patients survive longer than 2 years. PanNECs of large cell type are only marginally less aggressive than those of small cell type.

20.12 Inherited Syndromes

PanNETs can occur in the context of four inherited syndromes: multiple endocrine neoplasia type 1 and type 4 (MEN1, MEN4), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and the tuberous sclerosis complex (TSC) (Table 20.7). All are autosomal dominant tumor syndromes. PanNETs are most frequent in patients with MEN1, significantly less common in VHL, and rare in NF1 and TSC. The most common PanNETs occurring in MEN1 are nonfunctioning. Gastrinomas, though frequent in MEN1 (54% of neuroendocrine tumors), are usually duodenal, not pancreatic, in origin. Many PanNETs are multihormonal but with one dominant hormone, most commonly glucagon, followed in decreasing frequency by pancreatic polypeptide, insulin, somatostatin, and rarely other hormones. PanNETs account for a significant proportion of MEN1-related deaths, and therefore they require careful management. In contrast, PanNETs are an uncommon cause of mortality in patients with VHL. Only 11–17% of these patients develop PanNETs, which are

Table 20.7 Pancreatic neuroendocrine tumors in inherited syndromes

Inherited syndrome	Gene (encoded protein)	Frequency of PanNETs	Type of PanNETs (in decreasing order of relative frequency)
MEN 1	*MEN1* (Menin)	30–75%	Nonfunctioning (including microadenomas) Gastrinoma (duodenal) Insulinoma Glucagonoma Other
MEN 4	*CDKN1B* (p27)	Unknown	Nonfunctioning
VHL	*VHL* (VHL)	11–17%	Nonfunctioning (>98%)
NF1	*NF1* (Neurofibromin)	0–10%	Somatostatinoma (mainly duodenal, rarely pancreatic)
TSC	*TSC2* (Hamartin) *TSC1* (Tuberin)	Uncommon	Nonfunctioning Functioning

Abbreviations: *MEN 1* multiple endocrine neoplasia type 1, *MEN 4* multiple endocrine neoplasia type 4, *NF1* neurofibromatosis type 1, *PanNET* grade 1–3 pancreatic neuroendocrine tumor, *TSC* tuberous sclerosis complex, *VHL* von Hippel-Lindau syndrome

almost invariably nonfunctioning and asymptomatic. Up to 60% of PanNETs in VHL contain clear cells or multivacuolated lipid-rich cells, focally or diffusely, which are immunopositive for CAIX. Neuroendocrine tumors in NF1 are almost exclusively somatostatinomas of the periampullary region. PanNETs, both functioning and nonfunctioning, have been reported in a small proportion of individuals with TSC. The main clinical features of the four inherited syndromes associated with PanNETs are summarized in Table 20.8.

MEN4 is a very rare tumor syndrome with a phenotype that is similar to MEN1. Hence, patients presenting with features suggestive of MEN1 but without *MEN1* mutations should be tested for *CDKN1B* mutations, which are the underlying gene defect in MEN4 [19].

Table 20.8 Extrapancreatic lesions in multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis complex

Inherited syndrome	Prevalence	Lesions
MEN 1	1:40,000–1:20,000	• Parathyroid hyperplasia/adenoma • Duodenal endocrine tumors • Cutaneous lesions (lipoma, angiofibroma) • Anterior pituitary adenoma (functioning/nonfunctioning) • Adrenocortical tumors (functioning/nonfunctioning) • Thymic and bronchial neuroendocrine tumors • Gastric ECL-cell hyperplasia/tumors • Central nervous system tumors • Soft tissue tumors
MEN 4	Very rare	MEN1-like phenotype: NETs in parathyroid glands, pituitary, pancreas, and rarely other sites (cervix, bronchus, stomach)
VHL	1:36,000	• Pheochromocytoma, paraganglioma • Renal cell carcinoma • Hemangioblastoma (central nervous system, peripheral/spinal nerves, retina) • NETs in ampulla, duodenum, gallbladder, common bile duct • Papillary cystadenoma of epididymis/broad ligament, mesosalpinx • Endolymphatic sac tumor • Cysts of adrenal gland, kidney, testis, ovary
NF1	1:2500–1:3000	• Cafe au lait spots • Neurofibroma • Malignant peripheral nerve sheath tumor • Axillary or inguinal freckling • Duodenal NET, gangliocytic paraganglioma • Pheochromocytoma • CNS tumors (pilocytic astrocytoma of optic nerve, brain stem glioma, cerebellar astrocytoma) • Bone lesions • Lisch nodules
TSC	7–12:100,000	• Facial angiofibromas • Periungual fibroma • Hypomelanotic macules • Connective tissue nevus • Subependymal astrocytoma • Retinal nodular hamartomas • Lymphangioleiomyomatosis • Renal angiomyolipoma • Bone cysts • Hamartomatous rectal polyps • Gingival fibromas

Abbreviations: *ECL* enterochromaffin like, MEN1 multiple endocrine neoplasia type 1, *MEN4* multiple endocrine neoplasia type 4, *NET* neuroendocrine tumor, *NF1* neurofibromatosis type 1, *TSC* tuberous sclerosis complex, *VHL* von Hippel-Lindau syndrome

20.13 Glucagon Cell Hyperplasia and Neoplasia

Glucagon cell hyperplasia and neoplasia (GCHN), also known as Mahvash syndrome, is an autosomal recessive inherited disorder caused by germline mutation of the *GCGR* (glucagon receptor) gene [20]. It is characterized by the presence of glucagon cell hyperplasia, glucagon cell microadenomas, and glucagon-producing macroscopically visible PanNETs [21, 22]. It is believed that germline mutation of *GCGR* results in the absence of glucagon signaling in the liver, which in its turn induces glucagon cell hyperplasia and subsequent glucagon cell neoplasia. The pancreas may be diffusely enlarged or of normal size and contains numerous enlarged, hyperplastic islets with increased numbers of α-cells. In addition, there are endocrine microadenomas and PanNETs which immunohistochemically consist almost exclusively of glucagon-producing cells (Fig. 20.32). The Ki67 index in these tumors is usually very low (<1%).

GCHN is an extremely rare disease, and only a few cases have been reported to date. While glucagon serum levels are usually elevated, not all patients with GCHN have glucagonoma syndrome. The disease is usually benign, although metastasis has been reported. Not all patients with GCHN have a *GCGR* mutation, and in those with wild-type *CGCR*, the pathomechanism of the disease remains unknown.

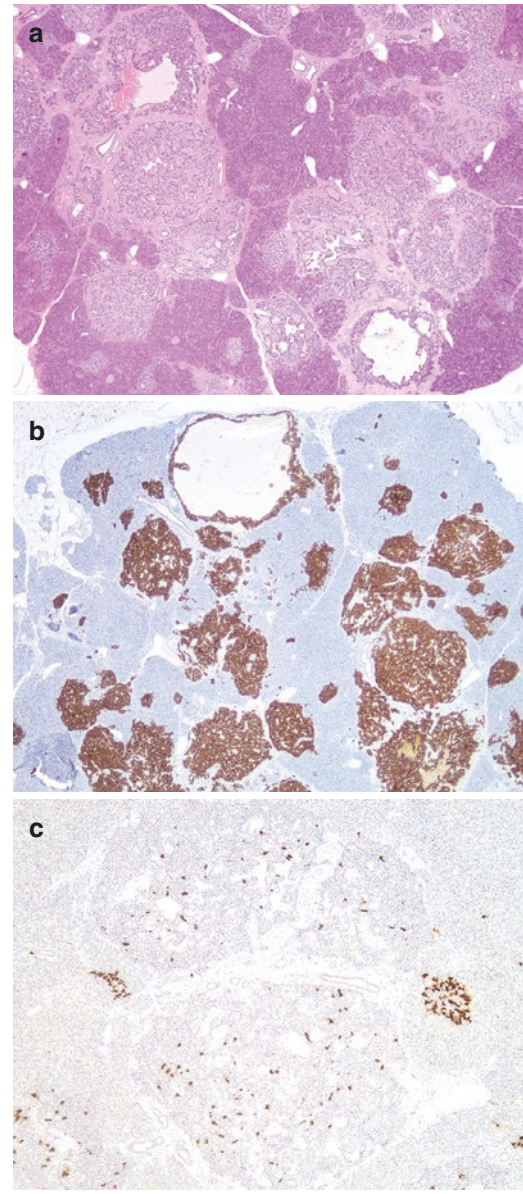


Fig. 20.32 Alpha-cell hyperplasia: islets appear more numerous than normal. They are enlarged and show some architectural irregularity. There is mild fibrosis in and around some of the abnormal islets. Note the presence of scattered normal-appearing islets (**a**). Immunostaining for glucagon demonstrates the predominance of α-cells in the enlarged islets. Note the normal number of α-cells in the unremarkable islets (**b**). Immunohistochemistry for insulin highlights the presence of very few β-cells within the hyperplastic islets, whereas a normal high number is present in unremarkable islets (**c**)

20.14 Insulinomatosis

Insulinomatosis is a condition characterized by the synchronous or metachronous occurrence of multicentric insulinomas causing hyperinsulinemic hypoglycemia [4]. Insulinomatosis usually occurs sporadically but has also been reported in a few kindreds and was recently linked to missense mutation of the gene encoding V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (*MAFA*) [23]. The insulinomas can be macrotumors or microscopically small tumors, but all express insulin exclusively (Fig. 20.33). In addition, small,

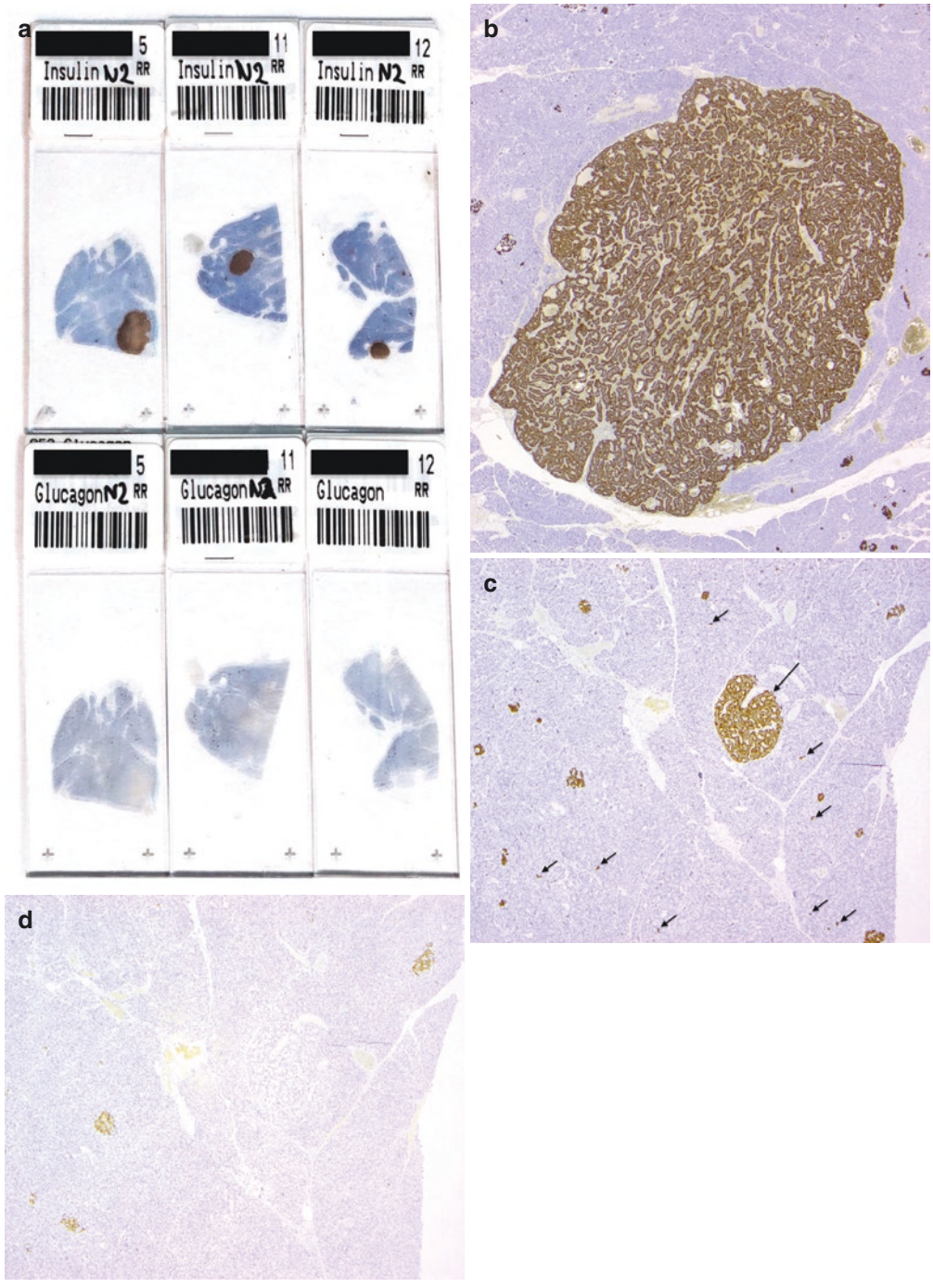


Fig. 20.33 Insulinomatosis: a distal pancreatectomy specimen contains three macroscopically visible PanNETs. On immunostaining, all three are positive for insulin and negative for glucagon (**a**: immunostaining for insulin [upper row] and glucagon [lower row]). All tumor cells show strong immunostaining for insulin (**b**). In addition to the three gross tumors, there are endocrine microadenomas that consist exclusively of β-cells (*long arrow*). Note the presence of scattered, small clusters of insulin-producing cells (*short arrows*) in addition to β-cells in normal islets (**c**). Immunostaining for glucagon is positive only in the islets of Langerhans, while the endocrine microadenoma and the small, scattered endocrine cell foci seen in (**c**) are negative (**d**)

proliferative, insulin-expressing monohormonal endocrine cell clusters have been described as the putative precursor lesions of the multifocal insulinomas. The tumors are usually benign, and metastatic spread is rare. The disease differs from solitary sporadic and MEN1-associated insulinomas.

20.15 Endocrine Microadenoma and Endocrine Microadenomatosis

An endocrine microadenoma of the pancreas is defined as a neuroendocrine neoplasm measuring less than 5 mm in size (Fig. 20.34). The features that distinguish an endocrine microadenoma from an enlarged nonneoplastic islet are the altered, usually trabecular, cell arrangement, the presence of a more prominent hyaline stroma, and the absence of the normal distribution of α-, β-, δ- and PP-cells in terms of cell numbers and localization within the islets of Langerhans (Fig. 20.35) (see Chap. 1, Sect. 1.4.4). In endocrine microadenomas, immunostaining for hormones is either absent or dominated by one islet hormone, with loss of the usual topographical distribution. Enlarged or aggregated islets in the context of chronic pancreatitis may exhibit an increased number of glucagon- and PP-producing cells, but the β- and δ-cells are always preserved, albeit in slightly reduced numbers (see Chap. 21, Fig. 21.1). Endocrine microadenomas are considered benign, but it is currently not known whether all or only some progress to clinically relevant PanNETs.

Endocrine microadenomatosis is defined as the presence of multiple, usually innumerable, microadenomas (Fig. 20.36). It is considered the hallmark of MEN1 but may also occur in patients with VHL, and, occasionally, in individuals without an apparent genetic syndrome. Multiple endocrine microadenomas that are exclusively composed of β-cells are seen in patients with insulinomatosis, who also develop multiple synchronous and metachronous macroscopic insulinomas. Endocrine microadenomatosis is to be distinguished from reactive islet clustering and enlargement (see above), from the diffuse type of islets normally present in the inferior part of the pancreatic head (see Chap. 1, Sect. 1.4.4) and from endocrine cell hyperplasia (see Chap. 21, Sect. 21.1).

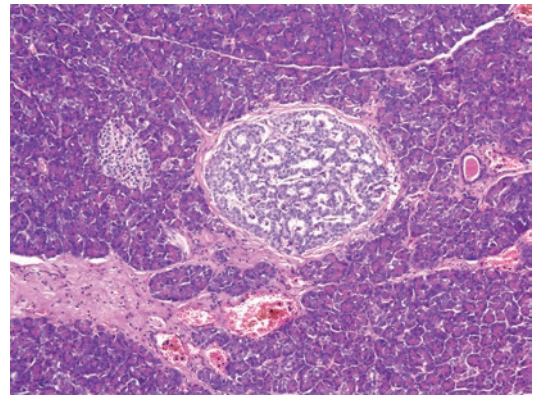


Fig. 20.34 Endocrine microadenoma: the increased size, trabecular cell arrangement, and surrounding thin sheath of fibrous stroma distinguish this endocrine microadenoma from an adjacent normal islet

20.16 Reporting Checklist

A reporting checklist of the data items to consider when reporting on pancreatic neuroendocrine neoplasia is provided in Table 20.9.

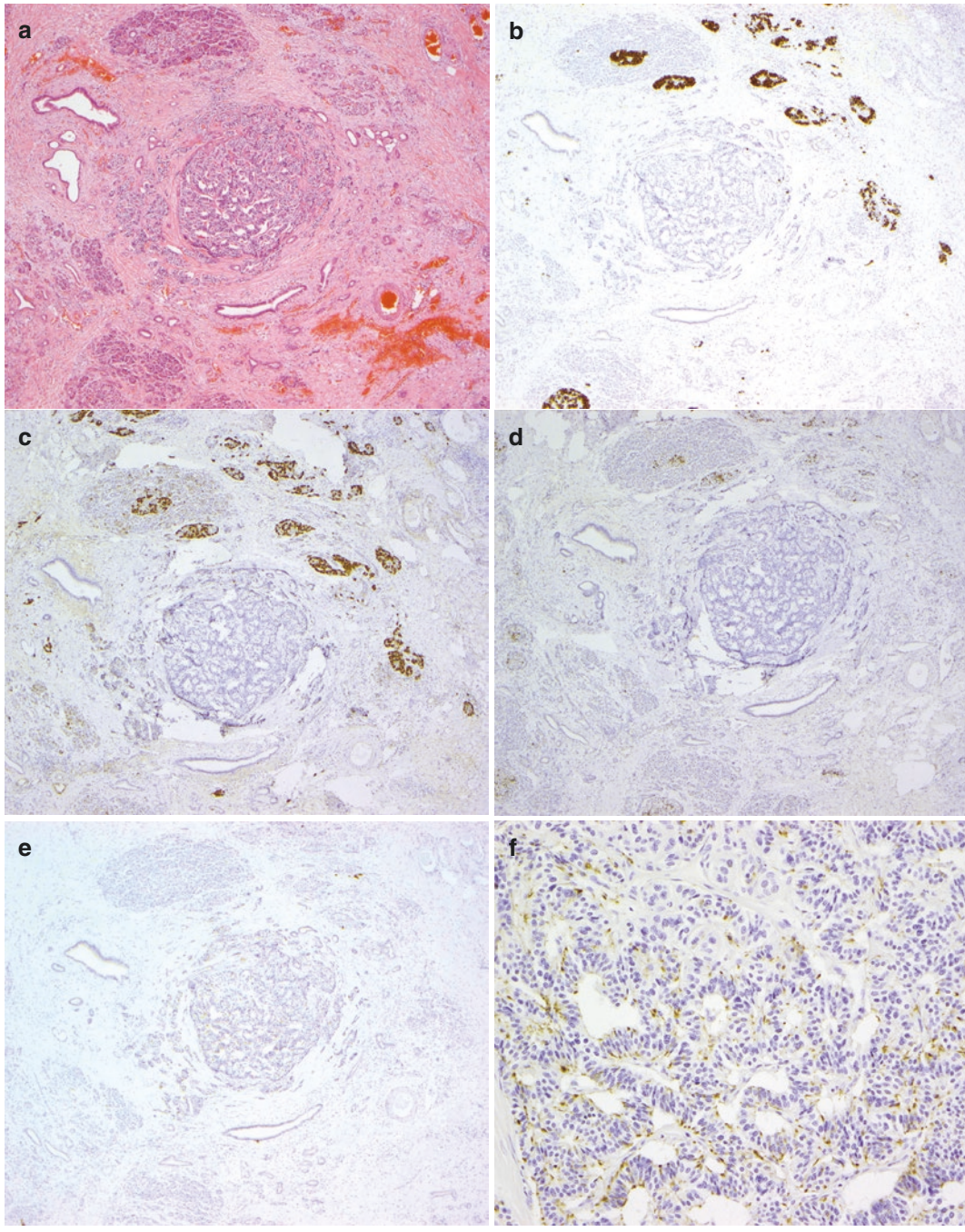


Fig. 20.35 Endocrine microadenoma: this incidentally identified endocrine microadenoma measures 0.8 mm in diameter and consists of monomorphous lesional cells that are arranged in a trabecular pattern. Note the increased fibrous stroma, especially in the periphery of the lesion (**a**). Immunostaining for insulin (**b**), glucagon (**c**), and somatostatin (**d**) is negative in the lesion but preserved in the surrounding islets of Langerhans. In contrast, all cells of the endocrine microadenoma show labeling for pancreatic polypeptide (**e** and **f**)

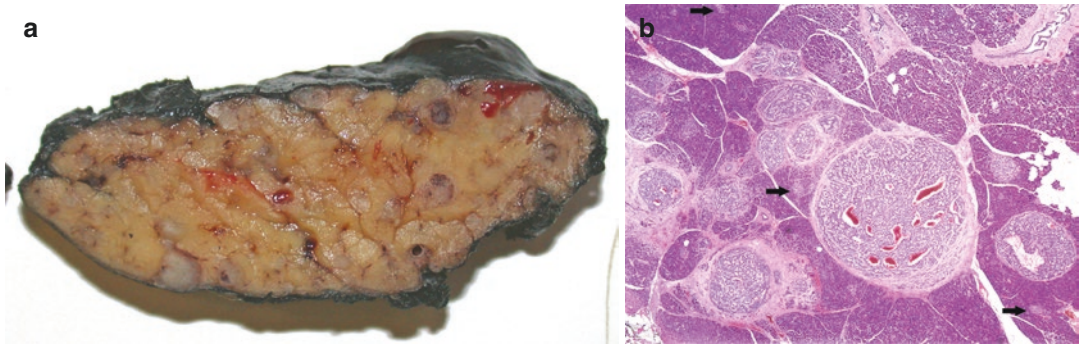


Fig. 20.36 Endocrine microadenomatosis: pancreatic parenchyma in this patient with MEN1 is studded with numerous well-circumscribed tumors, the vast majority of which measure less than 5 mm in size (**a**). Histologically, there are countless endocrine microadenomas. Note the presence of scattered normal-appearing islets (*arrows*) (**b**)

Table 20.9 Reporting checklist for pancreatic endocrine neoplasia

Microscopic assessment
• Specimen type (e.g., pancreatoduodenectomy, distal/total pancreatectomy, enucleation)
• Additional resected structures/organs (e.g., spleen, SMV)
• Tumor: – Unifocal/multifocal – Site – Size (3 dimensions) – Solid/cystic, color
Microscopic assessment
• Classification: – Pure neuroendocrine neoplasm Neuroendocrine tumor Neuroendocrine carcinoma – Mixed tumor (MiNEN): Mixed with ductal adenocarcinoma Mixed with acinar cell carcinoma Proportion of each component (in %)
• Differentiation: – Well-differentiated – Poorly differentiated
• Grade (based on WHO classification 2019): – Low – Intermediate – High
• Morphological variant
• Local tumor extent (e.g., limited to pancreas, or invasion of duodenum/ampulla, common bile duct, peripancreatic soft tissue, spleen, SMV, splenic vein)
• Tumor propagation: lymphatic, vascular, perineural
• Tumor metastasis: – Regional lymph nodes (location, number involved, total number) – Extraregional lymph nodes (location, number involved, total number) – Other

Table 20.9 (continued)

Microscopic assessment
• Completeness of resection (nearest margin(s), minimum clearance)
• Staging: – pTNM (according to UICC 8th edition and/or ENETS) – Further descriptors (pLVPnR)
• Ancillary tests/Immunohistochemistry: – Neuroendocrine markers: confirmation of neuroendocrine differentiation – Ki67: proliferation index (or mitotic count, if higher than Ki67 index) – p53, RB1, p16 – Hormones: Stained for/positive Clinically functioning tumor? – Markers of non-endocrine differentiation (in MiNEN): Adenocarcinoma (e.g., mucin stains, MUC1/2, CK19) Acinar cell carcinoma (e.g., trypsin, chymotrypsin, BCL10)
• Background changes (e.g., multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis 1)

Abbreviations: *ENETS* European Neuroendocrine Tumour Society, *G* grade, *MiNEN* mixed neuroendocrine—non-neuroendocrine neoplasm, *SMV* superior mesenteric vein, *UICC* International Union Against Cancer

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Further Reading

Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103:153–71.