Pathological Evaluation and Classification of Digestive Neuroendocrine Tumours

6

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6.1 The Pathological Diagnosis of Digestive NET

Neuroendocrine neoplasms (NEN) arise from neuroendocrine cells which are distributed in the mucosa of the gastrointestinal (GI) tract and in the pancreas. There are several diagnostic tools to perform the diagnosis of NEN, including imaging, serological tests and endoscopy, but the diagnosis should be formally confirmed by the pathological investigation. The histological feature of NEN, which is generally characteristic in most cases, at least for well-differentiated NEN, must be confirmed by immunohistochemistry and allows to categorise these tumours as NETs (neuroendocrine tumours) or NECs (neuroendocrine carcinomas) according to the last international WHO classification [5]. This is very important to assess the tumour prognosis and to guide patient therapy.

6.1.1 Morphology

Characteristic histopathological features of digestive NEN are held in common. By morphology, there is a clear distinction to be made, in all digestive locations, between the well-differentiated and the poorly differentiated tumours. This distinction is important, since their morphology, prognosis and response to treatments are very different. However, it must be emphasised that a relatively small percentage of tumours is not easy to classify into the well- or poorly differentiated groups, because they share some morphological characteristics of both of them. Well-differentiated tumours (called "neuroendocrine tumours", NET, according to the WHO 2010 classification, as discussed below) are composed of tumour

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cells possessing round nuclei with "salt and pepper" chromatin [5]. Their cytoplasm is eosinophilic and granular. They show regular insular, trabecular or sheet-like patterns, depending on the site of primary, the insular pattern being more frequent in the ileum, with palisading of the peripheral cell layers. Poorly differentiated tumours (called "neuroendocrine carcinomas", NEC, according to the WHO 2010 classification, as discussed below) are classified as small or large-cell carcinomas, according to the histological morphology of their cells [5]. The small cells are, as their name implies, small, round ovoid or spindle-shaped, with very scant cytoplasm; their chromatin is fine and granular without nucleoli. In contrast, large-cell carcinomas are composed of medium-sized or large-sized cells; their nuclei are atypical with evident nucleoli. These morphological characteristics are similar to those used to classify the lung neuroendocrine tumours according to the lung WHO 2004 classifications [50].

6.1.2 Immunohistochemistry

The morphological diagnosis of digestive NEN must be confirmed by immunohistochemistry, as firstly proposed by the European Neuroendocrine Tumor Society (ENETS) and confirmed by the WHO 2010 classification [40–42]. NEN share marker proteins with the neural cell system, such as synaptophysin and neuron-specific enolase. Among the several neuroendocrine markers, chromogranin A and synaptophysin are the most common and those which are required to confirm the diagnosis of NEN according to the ENETS recommendations and to the WHO 2010 classification of digestive tumours [5, 41, 42]. The neural cell adhesion molecule CD56 (NCAM) is also useful, especially in poorly differentiated tumours, because they may weakly, or not at all, express chromogranin A. Hindgut rectal NEN may be negative for chromogranin A and only express chromogranin B. The diagnosis of rectal NET should not be ruled out in the case of negativity of chromogranin A.

6.2 The Pathological Classification of Digestive NET

A new classification of digestive NEN has been formulated in the 2010 revision of the WHO classification of tumours of the digestive system [5]. The terminology and principles were greatly modified in this novel classification as compared to those used previously. Three main grading categories are recognised, irrespective of the site in the digestive system (neuroendocrine tumour Grade 1, neuroendocrine tumour Grade 2 and neuroendocrine carcinoma of small- or of large-cell types) combined with a site-specific TNM staging, which was published in 2009 by the AJCC-UICC following a 2006 TNM proposal by the European Neuroendocrine Tumor Society (ENETS) [41, 47].

6.2.1 The WHO 2010 Classification

6.2.1.1 Introduction

In 2000, the WHO published a classification for the histological typing of digestive neuroendocrine tumours (NETs) [48]. This classification remained unchanged following the WHO 2004 revision and was used until 2010 [9]. A new WHO classification for GEP-NET appeared in 2010 [5]. In the first pages of the WHO classification book, the "nomenclature and classification of neuroendocrine neoplasms of the digestive system" is introduced and described in detail [40]. Its main principle is a clear distinction between histological classification (including grading, the same in any digestive location) and staging (using the AJCC-UICC TNM 7th edition, specific for each location). As for most other tumour types, histological WHO must be associated with TNM staging since WHO and TNM complement each other.

According to the WHO 2010 classification, digestive neuroendocrine neoplasms (the term "neuroendocrine neoplasm or NEN" encompasses well- and poorly differentiated tumours) are classified into three main histological categories (Table 6.1): *neuroendocrine tumours grade 1 or NET G1* (Fig. 6.1a, b), *neuroendocrine tumours grade 2 or NET G2* (Fig. 6.1c, d) and *neuroendocrine carcinomas or NEC*, with two different subtypes, *of large- or small-cell types*; these poorly differentiated carcinomas are of grade G3 (Fig. 6.1e). This parallels well with the pulmonary neuroendocrine WHO classification [50]. Two other categories include *mixed adenoneuroendocrine carcinomas (MANECs) and hyperplastic and preneoplastic lesions*. The WHO 2010 classification deleted the terms "benign" and "malignant" used in the previous classification to describe the well-differentiated tumours assuming neuroendocrine neoplasms (NEN) as a category to be potentially malignant.

6.2.1.2 Basis of the Grading

The histological grading into G1, G2 and G3 is performed on the basis of the assessment of the proliferation fraction according to the ENETS scheme firstly published in 2006 [41], with the same cut-off values (Table 6.2). However, subtle differences appeared in the way to count. Indeed, in the WHO 2010 classification, it is required to count mitosis in 50 HPF (high-power field) (1 HFP = 0.2 mm^2), instead of 40 HPF in the ENETS proposals. It is recommended to count the Ki-67 index using the MIB

Table 6.1 General neuroendocrine neoplasm categories in the WHO 2010 classification

1	Neuroendocrine tumour, NET G1 (carcinoid)
2	Neuroendocrine tumour, NET G2
3	Neuroendocrine carcinoma, NEC (small- or large-cell type)
4	Mixed adenoneuroendocrine carcinoma, MANEC
5	Hyperplastic and preneoplastic lesions

Adapted from Bosman et al. [5]

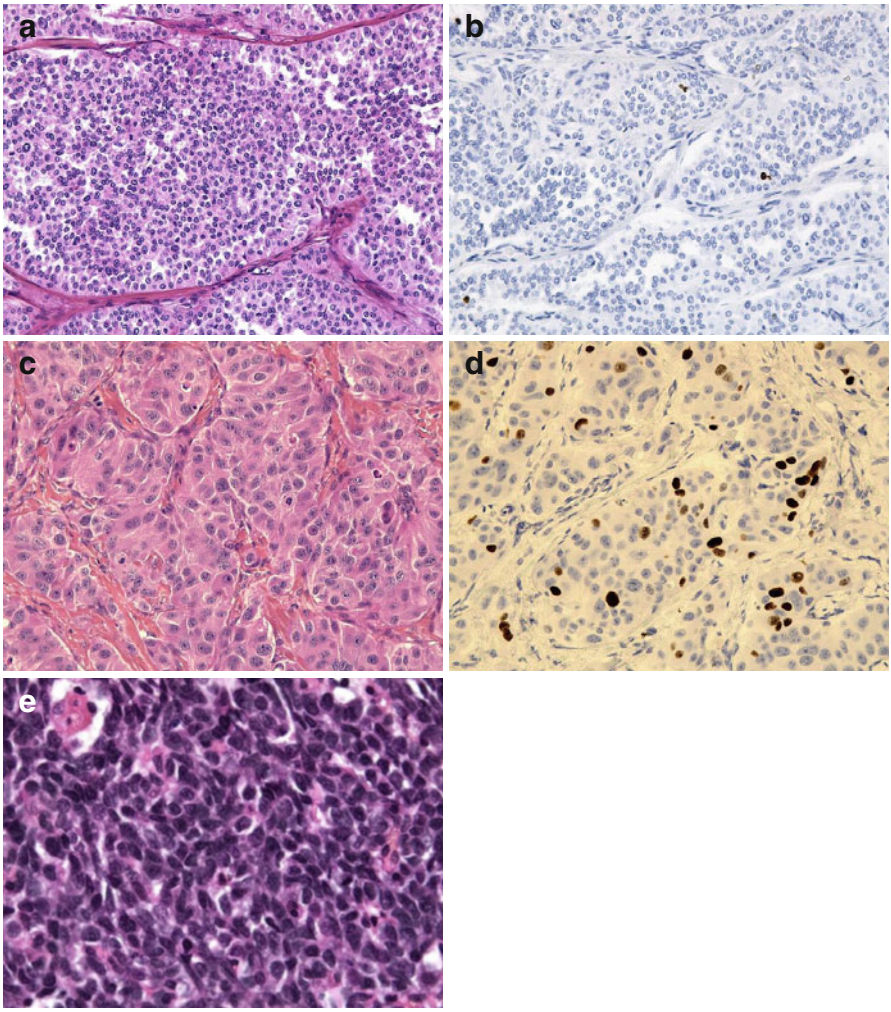

Fig. 6.1 A well-differentiated (**a**) neuroendocrine tumour (NET) of grade G1 (Ki-67 < 1 %, **b**); a well-differentiated (**c**) neuroendocrine tumour (NET) of grade G2 (Ki-67 = 12 %, **d**); a gastric small-cell poorly differentiated (**e**) neuroendocrine carcinoma (NEC)

antibody as a percentage of 500–2,000 cells (whereas it was recommended to count 2,000 cells in the ENETS proposals). Grade 1 tumours have a mitotic count <2 per 2 mm^2 (10 HPF) and/or ≤2 % Ki-67. Grade 2 tumours have a mitotic count between 2 and 20 per 2 mm^2 and/or 3–20 % Ki-67 >20 %. Grade 3 tumours have a mitotic count >20 per 2 mm^2 and/or Ki-67. If grade differs for mitosis and Ki-67 evaluation, it is suggested to consider the higher grade. It is of importance to note that in order to perform a proper evaluation of the mitotic count, the pathological specimen must have a minimal size: indeed, 50 HPF represents 10 mm^2. This is not feasible in a biopsy specimen where evaluation of Ki-67 is consequently required. The

Table 6.2 Grading for digestive neuroendocrine tumours, according to the WHO 2010 classification

Grade	Mitotic count (/2 mm²)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

Adapted from Rindi et al. [41] and Bosman et al. [5]
[a]10 high-power field [HPF], 40× magnification = 2 mm². It is recommended to count mitoses in at least 50 fields at ×40 magnification in areas of highest mitotic density and to divide the total number of mitoses by 5
[b]MIB1 antibody; % of 500–2,000 tumour cells in areas of highest labelling

prognostic value of this grading was demonstrated for foregut, midgut and hindgut NET [10, 13, 17, 18, 27, 35, 36, 45, 52]. Since the use of the WHO 2010 classification, several publications have pointed differences in the evaluation of tumour proliferation by Ki-67 or mitosis. There is a lack of concordance between grades assigned by both methods, the mitotic count being often lower than the Ki-67 count [19]. The best method to evaluate Ki-67, for example, is the use of manual or digital counting, and the best cut-off to discriminate between G1 and G2 still remains controversial [1, 11, 33, 49]. It has been recently suggested that Ki-67 is a better prognosis marker and predictor of metastases than mitoses [30].

6.2.1.3 Definition of the Five Categories of the WHO Classification

1. Neuroendocrine tumours grade 1: these tumours are well differentiated and possess a low proliferation rate, of grade G1 (see above). The term "carcinoid tumour" can be used in place of NET G1. This term was removed from the WHO 2000 classification, and it is important to recall that it is also used to designate neuroendocrine tumours of ileal origin, secreting serotonin, and often responsible for a carcinoid syndrome. "Carcinoid tumours" have a benign connotation, but it is well known that NET G1 can be malignant and metastatic, as it is observed in the lung (Fig. 6.2).
2. Neuroendocrine tumours grade 2: these tumours are well differentiated and possess an intermediate proliferation rate, of grade G2 (see above). The term "atypical carcinoid" is not recommended in the WHO 2010 classification; it cannot be used for NET G2.
3. Neuroendocrine carcinomas of large or small cells: these tumours are poorly differentiated and malignant, composed of small or large cells expressing the neuroendocrine markers chromogranin A and synaptophysin (staining might be faint or focal). They are of grade G3. The large-cell category was not included in the previous WHO 2000 classification. The small-cell category looks like the pulmonary "small-cell carcinoma" subgroup. All practitioners must be aware of the NEC category. Indeed, in the previous WHO classification, the term "carcinoma" was also used for well-differentiated tumours presenting metastases and/or invading the muscular layer in the digestive tract. It is important to document

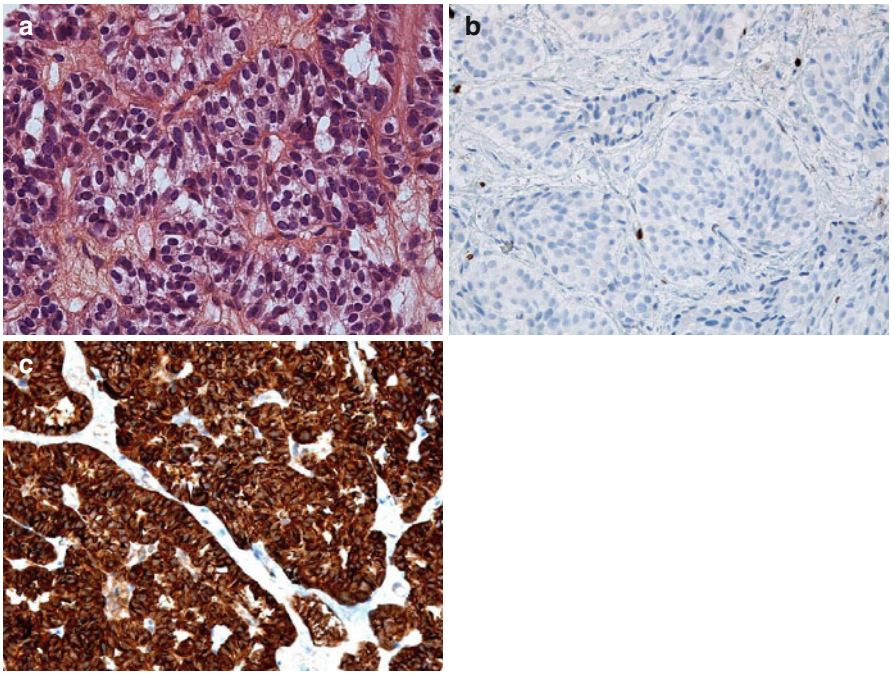

Fig. 6.2 Liver metastasis of a well-differentiated (**a**) pancreatic neuroendocrine tumour (NET) of grade G1 with a very low Ki-67 index <1 % (**b**) and a strong chromogranin A expression (**c**)

the tumour differentiation in the pathology reports in order to make impossible such error. Another important issue is the relationship between the grade G3 and the differentiation in this category. Indeed, the WHO classification suggests that all G3 tumours are poorly differentiated carcinomas. However, it is now known that the G3 group is heterogeneous, containing both well-differentiated NET and poorly differentiated NEC, the former being less aggressive with a lower Ki-67 index and a lower response rate to cisplatin-based chemotherapy [51]. It is not possible to classify "well-differentiated G3" tumours according to the WHO classification.

4. MANECs (mixed adenoneuroendocrine carcinomas) have both a neuroendocrine and an exocrine glandular phenotype. Thirty per cent of each component must be at least identified for this definition. The new term "MANEC" replaces the previous "mixed endocrine-exocrine tumour". Theoretically, the neuroendocrine component may be well or poorly differentiated. The exocrine component may be composed of acinar carcinoma cells. The frequency of MANEC and the type of exocrine or neuroendocrine component depend on the location in the digestive system. For example, in the colon, MANECs are more frequent and they often contain a poorly differentiated neuroendocrine component [28].
5. Hyperplastic and preneoplastic lesions.

6.2.2 The 2009 AJCC-UICC TNM

6.2.2.1 Introduction

In 2009, the 7th edition of the American Joint Cancer Committee-Union Internationale Contre le Cancer (AJCC-UICC) TNM classification was published [47], including for the first time digestive neuroendocrine tumours. It followed the first TNM classification which was proposed in 2006 (for NET of the stomach, duodenum and pancreas) and in 2007 (for NET of the ileum, colon/rectum and appendix) by a working group of the European Neuroendocrine Tumor Society (ENETS) [41, 42]. In the AJCC-UICC classification, high-grade (poorly differentiated) NECs are classified separately, by using the exocrine classification established in respective sites. When considering well-differentiated NETs, the AJCC-UICC TNM is similar to the previous ENETS/TNM proposals for intestinal anatomical sites but differs for other locations (the pancreas, stomach and appendix). It is important to document the pathological features, such as invasion and tumour size, to allow the translation of the staging between the classifications [23].

6.2.2.2 TNM Staging in the Different Digestive Locations

See Table 6.3 for details and comparison between UICC and ENETS T categories.

Table 6.3 T categories in the UICC and ENETS classifications of digestive neuroendocrine tumours, in the pancreas, stomach, small intestine, appendix and colon/rectum

Pancreas-ENETS		Pancreas-UICC[a]
T1	Tumour confined to pancreas, ≤2 cm	Idem
T2	Tumour confined to pancreas, 2–4 cm	Tumour confined to pancreas, >2 cm
T3	Tumour confined to pancreas and >4 cm or invading duodenum or bile duct	Tumour extends beyond pancreas, without involvement of coeliac axis or superior mesenteric artery
T4	Tumour involves coeliac axis or superior mesenteric artery or adjacent organs (stomach, spleen, colon, adrenal)	Tumour involves coeliac axis or superior mesenteric artery
Stomach-ENETS		Stomach-UICC
Tis	In situ/dysplasia (<0.5 mm)	Idem
T1	Tumour invading mucosa or submucosa, ≤1 cm	Idem
T2	Tumour invading muscularis propria or subserosa or >1 cm	Tumour invading muscularis propria or >1 cm
T3	Tumour penetrating serosa	Tumour invading subserosa
T4	Tumour invading adjacent structures	Tumour penetrating serosa or invading adjacent structures
Small intestine-ENETS		Small intestine-UICC
T1	Tumour invading mucosa or submucosa, ≤1 cm	Idem
T2	Tumour invading muscularis propria or >1 cm	Idem

(continued)

Table 6.3 (continued)

Small intestine-ENETS		Small intestine-UICC
T3	Jejunum, ileum: tumour invading subserosa Ampulla, duodenum: tumour invading pancreas or retroperitoneum	Idem
T4	Tumour invading serosa or other organs	Idem
Appendix-ENETS		Appendix-TNM[b]
T1	Tumour ≤1 cm; invading submucosa, muscularis propria	T1a: ≤1 cm T1b: >1–2 cm
T2	Tumour ≤2 cm; invading submucosa, muscularis propria, minimally (≤3 mm) subserosa/mesoappendix	Tumour >2–4 cm or invading the cecum
T3	Tumour > 2 cm or largely (>3 mm) invading subserosa/mesoappendix	Tumour >4 cm or invading the ileum
T4	Tumour invading serosa or other organs	Idem
Colon/rectum-ENETS		Colon/rectum-UICC
T1	Tumour invading mucosa or submucosa, T1a < 1 cm, T1b: ≥1–2 cm	Idem
T2	Tumour invading muscularis propria or >2 cm	Idem
T3	Tumour invading subserosa or mesorectum	Idem
T4	Tumour penetrating serosa or invading adjacent structures	Idem

Adapted from Rindi et al. [41], Rindi et al. [42], Sobin et al. [47], Bosman et al. [5]
According to UICC, the poorly differentiated NECs are classified as exocrine tumours
[a]According to UICC, all pancreatic neuroendocrine neoplasms (including G1, G2 and G3 and well- or poorly differentiated tumours) are classified following the pancreatic exocrine tumour classification
[b]Goblet cell carcinoids are classified according to the exocrine carcinoma classification

Pancreas

In this location, the AJCC-UICC applies the same TNM as the one used for classifying adenocarcinomas, either for well-differentiated or poorly differentiated tumours. In the AJCC-UICC TNM, invasion of the peripancreatic fat applies to pT3 tumours as compared to tumour size >4 cm in the ENETS TNM (Table 6.3). The size cut-off of 4 cm, which is reported to be an important prognostic factor [45], is not included in the AJCC-UICC classification. There is a discrepancy between the ENETS and UICC staging in the pancreas in a large proportion of cases [29].

Stomach

In this location, a Tis stage is defined (in situ tumour, less than 0.5 mm). The UICC and ENETS classifications differ. Tumours invading the subserosa are T2 according to ENETS and T3 according to UICC.

Intestine

The UICC and ENETS classifications are identical in the small intestine. The T2 and T3 stages apply to tumours invading the muscularis propria and the subserosa,

respectively, whereas T4 tumours penetrate the serosa (Table 6.3). In the rectum, the stage and grade according to ENETS/WHO are correlated with survival (Weinstock).

Appendix

According to the UICC classification, the tumour size is a very important criterion to classify NET in this location. According to ENETS, the invasion into the mesoappendix should be evaluated to distinguish T2 and T3 tumours (T3 tumour >2 cm and/or >3 mm extension into the mesoappendix).

Colon/Rectum

In the colon and rectum, the UICC and ENETS classifications are identical. T1 is separated into T1a and T1b, according to size (<1 cm or ≥1–2 cm). This parameter is important for endoscopic resection of rectal tumours.

6.3 Specificities of Pathological Diagnosis According to the Digestive Locations

6.3.1 Pancreas

Pancreatic NETs represent a very heterogeneous group of tumours, depending on functional status, presence of inherited syndromes or tumour differentiation [21, 22]. By definition, tumours are greater than 5 mm (below this size, they are defined as microadenomas). Functional tumours are associated with clinical syndromes caused by inappropriate secretion of insulin, glucagon, somatostatin, gastrin or VIP. Non-functioning tumours are often discovered incidentally, or when they become clinically apparent due to their large size, to invasion of adjacent organs or to the occurrence of metastases. Most PNETs are solitary and well differentiated; when multiple, MEN1 or VHL syndromes should be suspected. Well-differentiated NETs are usually well circumscribed; they may present different histological patterns (such as solid, trabecular, gland-like, oncocytic); they may show invasion of the peripancreatic fatty tissue (then classified as T3 according to UICC TNM, see above). First metastases are usually found in regional lymph nodes and the liver. Poorly differentiated NECs are infrequent in the pancreas, mostly represented by large-cell NEC [3].

Among functional pancreatic NETs, insulinomas are the most frequent. In 4–6 % of cases, they are associated with MEN1 [25]. They are frequently discovered while still small, and most are less than 2 cm, due in part to their earlier detection [26]. A relatively characteristic histological feature is the stroma with deposition of amyloid. Pancreatic gastrinomas are associated with the sporadic form of Zollinger-Ellison syndrome, as compared to duodenal ones which are more frequent, smaller and more often associated with MEN1 syndrome [25]. The histological aspect of gastrinomas has no distinctive features with other functioning or non-functioning pancreatic NETs (Fig. 6.3). Glucagonomas are usually large and solitary tumours more frequent in the tail. They cause a functional syndrome including a skin rash (necrolytic migratory erythema). They represent 8–13 % of functioning tumours.

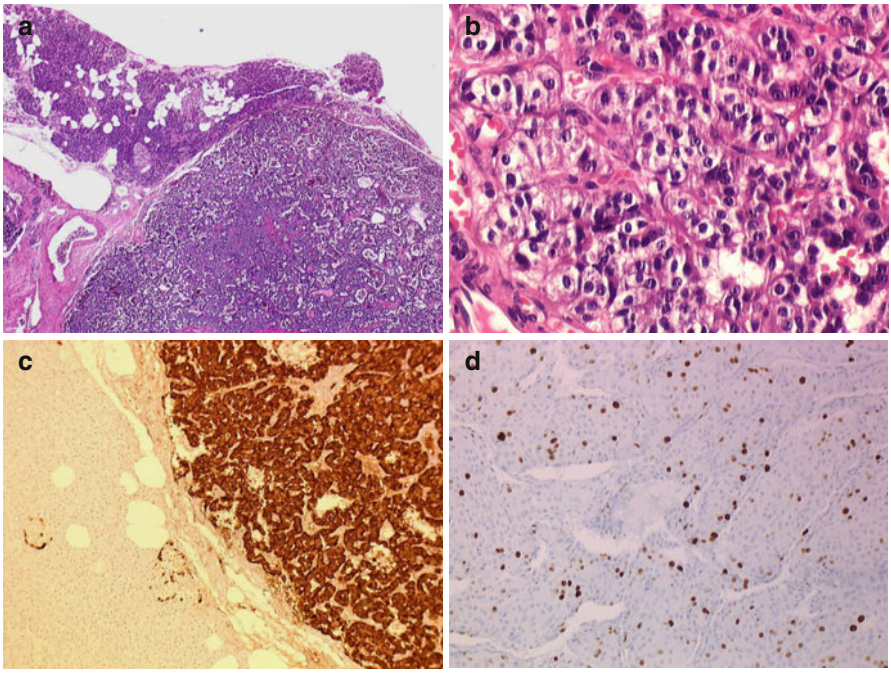

Fig. 6.3 A pancreatic glucagonoma corresponding to a well-differentiated neuroendocrine tumour (NET) G2 at low (**a**) and high (**b**) magnification. Tumour cells are regular and strongly express glucagon (**c**). Ki-67 is calculated at 6 % (**d**)

Inherited diseases, mostly MEN1 and VHL disease, are responsible for multiple PNETs, associated with microadenomas, which are more frequent and numerous in MEN1 (Fig. 6.4).

In VHL disease, pancreatic NETs occur in about 10–17 % of patients, whereas VHL is prevalent in about 0.5 % of pancreatic NETs [4, 7, 12]. The presence of microadenomas is not constant in pancreatic specimen resected for NET (about 70 % of cases) [37]. As compared to sporadic NET, VHL-NETs present a lower malignancy rate [12].

6.3.2 Stomach

Well-differentiated gastric NETs are classified into types 1, 2 and 3 [25, 43]. Type 1 NETs are the most common (70–80 %). They are related to fundic atrophic gastritis and hypergastrinaemia secondary to the deficient production of gastric acid. They occur in the fundus, are multifocal, small (mostly less than 1 cm) and polypoid, usually G1 tumours (Fig. 6.5). They are composed of enterochromaffin-like (ECL) cells and associated with ECL-cell hyperplasia in the adjacent mucosa. The prognosis of type 1 gastric NET is excellent; their small size allows an endoscopic resection in most cases. Type 2 tumours are rare. They are associated with a

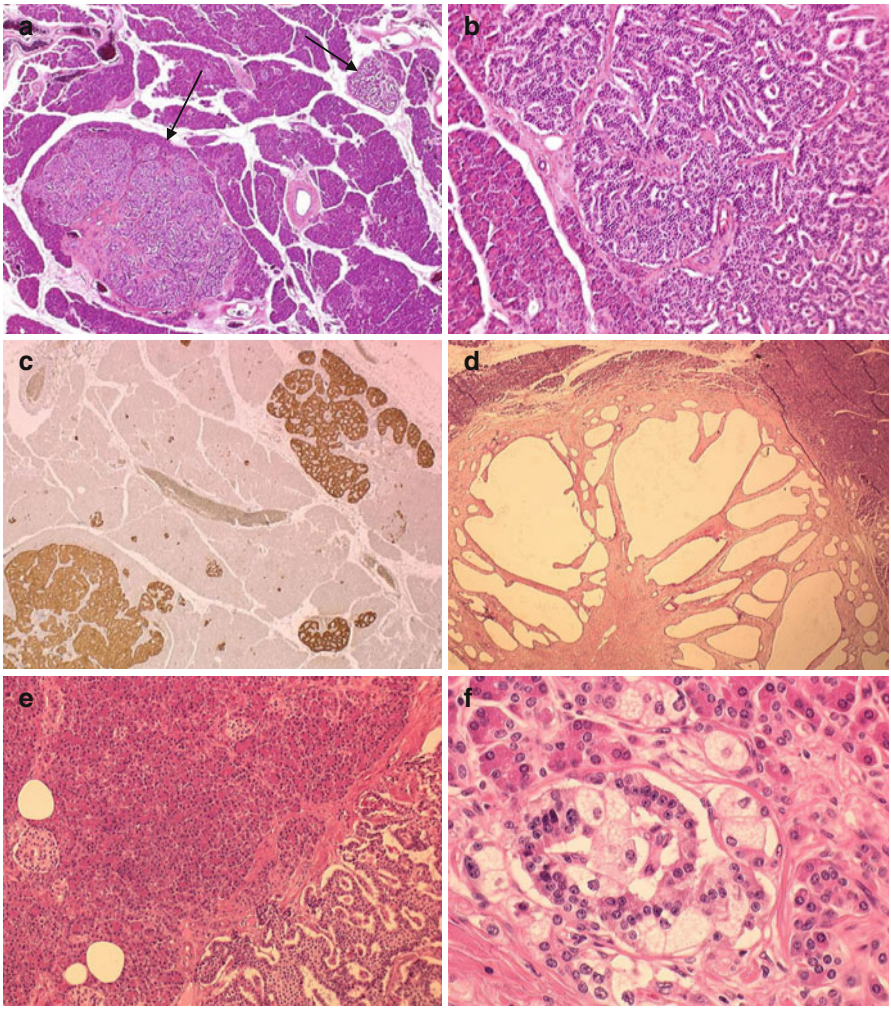

Fig. 6.4 Two pancreatic microadenomas (**a**, *arrows*) in a patient with multiple endocrine neoplasia type 1, well delimited and composed by regular cells (**b**) expressing chromogranin A (**c**). A serous cystadenoma (**d**), a well-differentiated neuroendocrine tumour of grade G1 (**e**) and a small microadenoma containing large neuroendocrine clear cells (**f**) in patient with a von Hippel-Lindau disease

Zollinger-Ellison syndrome. Hypergastrinemia causes fundic ECL-cell hyperplasia and, in the setting of MEN1, small fundic neuroendocrine tumours which are numerous and multifocal. Type 2 tumours are very similar to type 1 tumours but not associated with fundic atrophic gastritis. Moreover, lymph node metastases are more frequent than in type 1 NET [25, 43]. Type 3 NETs occur in any part of the stomach and are not associated with atrophic gastritis, hypergastrinemia, ECL-cell hyperplasia or MEN1. They are well-differentiated, solitary and larger than type 1 or type 2 tumours, with a more aggressive course and more frequent local or distant

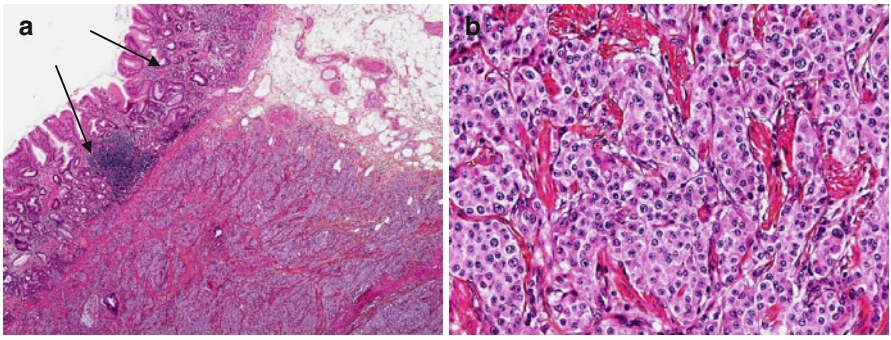

Fig. 6.5 A type 1 gastric NET (**a**, see the overlying inflammatory fundic mucosa, *arrows*), measuring 1.5 cm and infiltrating the submucosa (pT2, according to UICC TNM), well-differentiated (**b**) of grade G1

metastases [44]. Type 4 gastric NEN are poorly differentiate, large, ulcerated tumours of poor prognosis, occurring in any part of the stomach [25]. Poorly differentiated NECs are rare in the stomach.

6.3.3 Small Intestine

6.3.3.1 Ileum

Most of the ileal NETs are serotonin-producing EC-cell tumours. A carcinoid syndrome, due to the effect of serotonin, is present when tumours are of significant size, usually with liver metastases. These NETs are not associated with any of the known inherited syndrome (i.e. MEN1, von Hippel-Lindau disease, neurofibromatosis, etc.). However, familial cases have been described [16, 20]. Ileal NETs occur in the distal part of the ileum and can present as multiple tumours in some cases [53]. Histologically, they present an insular growth pattern with frequent palisading at their periphery and a fibro-sclerotic stroma. They often deeply invade the intestinal wall and give lymph node and liver metastasis, whereas their proliferative index is usually low [18]. The presence of mesenteric tumour deposit is frequent and could be an indicator of poor prognosis and survival [15].

6.3.3.2 Jejunum

A recent study underlines the heterogeneity of jejunal NETs and supports the distinction between "upper" and "lower" jejunal tumours, which, for prognostic purposes, could be grouped with, respectively, duodenal and ileal NETs [8].

6.3.3.3 Duodenum

In the duodenum, well-differentiated NETs are of five main types: (1) gastrinoma or gastrin-producing NET with or without MEN1 syndrome, (2) somatostatinoma or somatostatin-producing NET with or without neurofibromatosis type 1, (3) non-functioning NET, (4) gangliocytic paragangliomas and (5) poorly differentiated NEC.

Non-functioning NET may produce gastrin, somatostatin, serotonin or calcitonin. Gastrin-producing NETs occur mainly in the proximal duodenum, whereas somatostatin-producing NETs occur mainly in the ampulla of Vater [14]. The somatostatinoma syndrome does not usually develop. Histologically, the pseudoglandular pattern with psammoma bodies is characteristic; a neurofibromatosis type 1 syndrome should be suspected. Both gastrin- and somatostatin-producing NETs can be associated with MEN1. In this case, hyperplasia of neuroendocrine cells can be found in the adjacent non-neoplastic mucosa. Most duodenal gastrinomas are confined to the mucosa and submucosa, but lymph node metastases are frequent and often much larger than the duodenal primary, whereas liver metastases are rare [2, 25]. Duodenal gastrinoma can be sporadic or associated with MEN1 (in 20–30 % of cases). They frequently metastasise to the regional lymph nodes, but liver metastases are less frequent than in patients with pancreatic gastrinomas. Gangliocytic paragangliomas possess a triphasic cellular differentiation with neuroendocrine cells, ganglion cells and Schwann-like cells. They mainly occur in the papilla of Vater, and their course is usually benign, but they may spread to a lymph node. Duodenal NECs, which are infrequent, most commonly occur in the papilla of Vater [25].

6.3.4 Colon/Rectum

Rectum NETs are more frequent than colonic NETs, often solitary, sessile and incidentally discovered on colonoscopy. They are increasing in incidence, probably due to increase reporting of small polyps at endoscopy. Average tumour size is <1 cm and G1 tumours account for >80 % of cases [52]. Large tumours may be ulcerated. Rectal NETs are usually negative for chromogranin A and positive for prostatic acid phosphatase (Fig. 6.6). They can be treated by endoscopic resection, depending on their size and on tumour invasion, as determined by endoscopic ultrasound (in general if <2 cm and no invasion of muscularis propria) [39]. The evaluation of the margin and of the grading is important in such specimen [52].

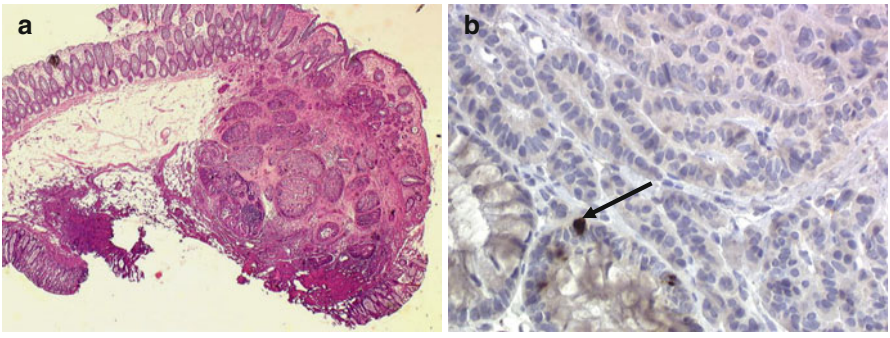

Fig. 6.6 A well-differentiated NET of the rectum, less than 1 cm and infiltrating the submucosa (pT1a), resected by mucosectomy (**a**). Chromogranin A is not expressed by tumour cells; in contrast, it is expressed by normal neuroendocrine cells located in the glands of the mucosa (**b**, *arrow*)

In the colon, NEC are more frequent than in the rectum. Large-cell NEC is the most common type [46]. Mixed tumours (MANEC) are not infrequent, and overlying adenoma or adenocarcinoma is associated with infiltrative poorly differentiated neuroendocrine carcinomas [28].

6.3.5 Appendix

Appendiceal NETs are frequent, often diagnosed after an appendiceal surgical rejection because of symptoms of acute appendicitis. Most are EC-cell NETs, comparable to ileal EC-cell NETs and arise in the tip (>70 % of cases) of the appendix [6]. Tubular carcinoid is a histological variant difficult to diagnose which should not be misdiagnosed as adenocarcinomas. The goblet cell carcinoid is classified, in the 2010 classification, according to the scheme for carcinoma [5]. Those tumours contain both neuroendocrine cells and cells with intracytoplasmic mucus similar to goblet cells, with a predominantly submucosal growth in a concentric manner. Goblet cell carcinoids are more aggressive than conventional NETs. Most conventional NETs of the appendix are less than 2 cm (>80 %) and infiltrate the appendix wall [38]. Poorly differentiated tumours are exceptional. The risk of metastases increases with size and deep invasion of the appendix. Moertel et al. reported metastatic disease in 31 % of patients with tumours > 2 cm [32]. Patients with tumours >2 cm should be treated by right hemicolectomy [34, 38]. The invasion of the mesoappendix is included in the ENETS TNM proposal (T3 if >3 mm; see Table 6.3), but not in the 2009 UICC TNM. Its prognostic impact is still controversial, but McGillivray et al. reviewed 414 appendiceal NETs and found that the mesoappendiceal invasion was related to metastatic disease [31].

Conclusion

Despite a certain degree of morphological and immunohistochemical homogeneity of well-differentiated digestive NETs, these tumours are heterogeneous regarding their presentation (functional status, presence of inherited syndromes), prognosis and staging according to their location in the digestive system. Because of frequent modifications in nomenclature, grading and staging, it is important to identify the minimal data that should be reported in all pathology reports in order to ensure optimal reproducible and uniform data to aid in both clinical management and stratification in therapeutic trials (Table 6.4) [40]. The use of the 2009 international UICC TNM is recommended, but in certain locations criteria of the ENETS classification should be added (e.g. the invasion of mesoappendix). The histological differentiation should clearly appear in order to avoid problems with the "carcinoma" category, different in the WHO 2000 and 2010 classification. It is important to give the exact value of proliferation rate to make comparison possible and to better stratify patient groups, since several data suggest to change the cut-off between G1 and G2. It is now clear that Ki-67 index is not optional and is very important especially in biopsy specimens, which do not allow to properly assess the mitotic counts [24]. It is important to standardise pathological diagnosis, grading and staging of NETs in the clinical management of patients and also to give a uniform basis for research trials.

Table 6.4 Indications for minimal data for the pathological report of neuroendocrine tumours

Diagnostic
Morphology, differentiation (well or poorly differentiated)
Immunohistochemistry (chromogranin A and synaptophysin expression)
Assessment of hormone expression upon specific clinical request
Classification
WHO 2010
Histological grade
Grade G1, G2 or G3
In addition, give the exact value of mitotic and/or Ki-67 index
In biopsy samples, use the Ki-67 index
pTNM
Size, exact site
Distance from resection margin (for resection specimen)
AJCC-UICC TNM 7th edition, 2009 (one may add ENETS/TNM in certain locations)

Adapted from Bosman et al. [5], Rindi et al. [40] and Klöppel et al. [24]

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