Belgian guidelines for pathology reporting of neuroendocrine neoplasms of the pancreaticobiliary and gastrointestinal tract.

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Abstract

Since neuroendocrine neoplasms are rare tumors, registration of patient data in national and multinational registries is recommended. Indeed, this will facilitate multicenter studies on the epidemiology, efficacy and safety of diagnostic and therapeutic strategies for well-differentiated neuroendocrine tumors as well as for neuroendocrine carcinomas. In Belgium, data on patient and tumor characteristics of all newly diagnosed malignancies have been collected in the Belgian Cancer Registry since 2004 including anonymized full pathological reports. The Digestive Neuroendocrine Tumor (DNET) registry collects information on classification, staging, diagnostic tools and treatment in a prospective national online database. However, the terminology, classification and staging systems of neuroendocrine neoplasms have changed repeatedly over the past 20 years as a result of a better understanding of these rare tumors, by joining forces internationally. These frequent changes make it very difficult to exchange data or perform retrospective analyses. For optimal decision making, for a clear understanding and to allow reclassification according to the latest staging system, several items need to be described in the pathology report. This paper provides an overview of the essential items in reporting neuroendocrine neoplasms of the pancreaticobiliary and gastrointestinal tract. (Acta gastroenterol. belg., **2023,** 86, **345-351**.

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Introduction

In 1907, S. Oberndorfer introduced the term carcinoid tumor ("karzinoide" or "carcinoma-like") to describe the unique feature of a midgut tumor having a relative monotonous structure and less aggressive behavior despite having some resemblance microscopically to intestinal adenocarcinoma (1). Subsequently, the term carcinoid has been used more generally, to describe both intestinal and extra-intestinal tumors with a characteristic morphology and staining pattern.

On macroscopy, most well-differentiated neuroendocrine tumors are well-demarcated, solid and white-yellow or pink-brown. On histology, the tumors show various organoid histological patterns, characterized by a nesting, trabecular, glandular, gyriform or pseudorosette arrangement of their cells. The tumor cells are relatively uniform, with a finely granular amphophilic to eosinophilic cytoplasm and a round to oval nucleus. The chromatin pattern is characteristically coarsely clumped ("salt and pepper").

Neuroendocrine cells are part of the neuroendocrine (cell) system, formerly called '*APUD (Amine Precursor Uptake and Decarboxylation) cell system'*. The term *APUD cell* was introduced by Anthony Pearse in 1966, and subsequently the terminologies *APUD tumors* and *APUDomas* came into use (2). The term *'APUD cell system'* was later expanded to include not only almost all the amine-hormone producing cells throughout the body, but also the peptide-hormone secreting cells, and was replaced by the term neuroendocrine system in 1978. The latter term is a collective name for all cells distributed in the body with a common characteristic of secreting amines (neurotransmitter-like molecules such as serotonin) and peptides with endocrine function (Amine and Peptide Hormones Secreting Endocrine Cells). Previously it was mistakenly thought that all these cells are derived from the neural crest. This was later disproven by showing that a great part of these cells originate from multipotent stem cells implanted in different body organs. Thus, the term "neuroendocrine cell" actually does not indicate a common embryological origin of neuroectoderm but refers to a common phenotype: expression of genes characteristic of neural cells as well as expression of genes characteristic of endocrine cells, with presence of synapse-like vesicles as well as neurosecretory-like dense-core granules. The neuroendocrine cell system comprises the neuroendocrine-type cells that are part of some endocrine organs (e.g. adrenal medulla) or that are part of some non-endocrine organs (e.g. pancreatic islets

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of Langerhans), as well as the diffuse neuroendocrine system, a scattered system of neuroendocrine cells, particularly important in the gastrointestinal (entero-endocrine cells) and respiratory tract. Most cells of the diffuse neuroendocrine system are derived from endodermal cells of embryonic gut or bronchial buds and most act in a paracrine manner. Neoplasms composed of neuroendocrine cells not only make various amine hormones and peptide hormones, but also express many types of peptide receptors on the cell membrane. The membrane receptors enable the tumor cells to respond to several growth factors, which, combined with genetic instability, probably contributes to the multifocal nature of these tumors.

Neuroendocrine cells are difficult to recognize in routine HE staining. Previously they were visualized by tissue treatment with silver salts with precipitation of black pigment. Dependent on the staining reaction that was used, they were called *argentaffin* or *argyrophilic cells* (3). Another old terminology is *enterochromaffin cells*, referring to precipitation of brown pigment in these cells in a reaction with chromium salts. These silver and chromium staining techniques are not used any more, hence also these older terms are no longer appropriate. Actually, more than 20 different hormone products secreted by these cells have been identified. In transmission electronmicroscopy they are recognized by the presence of secretory granules with an electron-dense core.

In 2000, the World Health Organization (WHO) established the use of "neuroendocrine tumor" over "carcinoid tumor" in its disease classification system, but this new definition has not been accepted by all practitioners and the term carcinoid is still in use in e.g. the respiratory system. Nowadays, in gastrointestinal clinical practice, the wording carcinoid is often reserved for small bowel neuroendocrine tumors linked to a carcinoid syndrome and still frequently used for gastric neuroendocrine tumors. Since the WHO 2000 edition, the terminology has been refined as a deeper understanding of this uncommon cancer was gained. The correct wording for all tumors composed of cells with neuroendocrine features nowadays is "neuroendocrine neoplasm (NEN)", encompassing well-differentiated neuroendocrine tumors (WD NET) and poorly-differentiated neuroendocrine carcinomas (NEC) (4). The term "carcinoid" with its largely incorrect benign connotation should be avoided. However, there is still confusion in the terminology surrounding neuroendocrine neoplasms. This can be seen amongst others in the ICD Oncology coding. Currently, the third edition, second revision is in use. Table 1 shows that the preferred wording used for code 8240/3 is 'neuroendocrine tumor', but low grade neuroendocrine carcinoma, well-differentiated neuroendocrine carcinoma, carcinoid and neuroendocrine tumor grade 1 are considered synonyms or related wordings, while the preferred term for 8249/3 seems to be neuroendocrine tumor grade 2, with as synonyms and related options: atypical carcinoid tumor, moderately-differentiated neuroendocrine carcinoma or neuroendocrine tumor grade 3. 8246/3 refers to neuroendocrine carcinoma, NOS. This last code is still sometimes inappropriately used by pathologists as soon as metastatic disease is found, also for well-differentiated tumors, as historically, according to the 2000 WHO classification, the term neuroendocrine tumor was reserved for non-metastatic neuroendocrine tumors and all metastatic well-differentiated neuroendocrine tumors were called well-differentiated neuroendocrine carcinomas.

In Belgium, pathology reports sent to the Belgian Cancer Registry include the CODAP (Codering van Diagnoses in de Anatomo-Pathologie; Flanders) or SNOMED (Systematized Nomenclature of Medicine Clinical Terms, Brussels/Wallonia) coding, which is converted at the Cancer Registry to the ICD-O coding (5).

Table 1. — **Examples of ICD-O-3.2 coding for neuroendocrine neoplasms: preferred term followed by synonyms/related terms**

8240/3 Neuroendocrine tumor, NOS
Carcinoid tumor, NOS
Carcinoid, NOS
Bronchial adenoma, carcinoid
Neuroendocrine carcinoma, low grade
Neuroendocrine carcinoma, well-differentiated
Neuroendocrine tumor, grade I
Typical carcinoid
8241/3 Enterochromaffin cell carcinoid
Argentaffinoma
Carcinoid tumor, argentaffin
EC cell carcinoid
Serotonin producing carcinoid
Serotonin producing tumor
8242/3 Enterochromaffin-like cell tumor, malignant
ECL cell carcinoid, malignant
8243/3 Goblet cell carcinoid
Mucinous carcinoid
Mucocarcinoid tumor
8244/3 Mixed adenoneuroendocrine carcinoma
Combined carcinoid and adenocarcinoma
Mixed carcinoid and adenocarcinoma
Composite carcinoid
MANEC
Mixed carcinoid-adenocarcinoma
8245/1 Tubular carcinoid
8245/3 Adenocarcinoid tumor
8246/3 Neuroendocrine carcinoma, NOS
Poorly differentiated neuroendocrine neoplasm
8247/3 Merkel cell carcinoma
Merkel cell tumor
Primary cutaneous neuroendocrine carcinoma (C44._)
8248/1 Apudoma
8249/3 Neuroendocrine tumor, grade 2
Atypical carcinoid tumor
Neuroendocrine carcinoma, moderately differentiated
Neuroendocrine tumor, grade 3

Table 2. — **WHO classifications**

WHO 2010	Mitoses/10 HPF*	Ki-67 Index*	WHO 2017	Mitoses/10 HPF*	Ki-67 Index*
Well-differentiated NENs			Well-differentiated NENs		
NET grade 1	< 2	< 3	NET grade 1	< 2	< 3
NET grade 2	2–20	3–20	NET grade 2	2–20	3–20
			NET grade 3	> 20	> 20
Poorly differentiated NENs			Poorly differentiated NENs		
NEC (small-cell or large-cell), grade 3	> 20	> 20	NEC grade 3 Small-cell type Large-cell type	> 20	> 20
MANEC			MiNEN*		

*MiNENs may have non-endocrine component other than adenocarcinoma, e.g., squamous cell carcinoma or acinar cell carcinoma. To qualify as MiNEN, each component must be at least 30%. HPF = high power fields, MANEC = mixed adenoneuroendocrine carcinoma, MiNEN = mixed endocrine non-endocrine neoplasm, NEC = neuroendocrine carcinoma, NEN = neuroendocrine neoplasm, NET = neuroendocrine tumor, WHO = World Health Organization

The Belgian Cancer Registry also receives information from newly diagnosed cancer patients through the 'Oncology Care Programs' (organized as a part of the National Cancer Plan 2008-2010), including the ICD-O coding. The Belgian Cancer Registry also follows the WHO blue books (4) and regularly discusses with the data managers in the hospitals.

Before the introduction of the Ki-67 proliferation index in the WHO classification, the concept well- and moderately-differentiated neuroendocrine tumor versus poorly-differentiated neuroendocrine carcinoma, small or large cell was already applied. The distinction with poorly-differentiated tumors was solely based on morphology. After having shown the prognostic value of the grading system on the basis of the Ki-67 index, it was introduced in the WHO classification in 2010, leading to a classification system based both on morphology and proliferation (4). The importance of morphology was emphasized when it was clearly shown that neoplasms with a high Ki-67 index can be well- or poorly-differentiated, with a need for different treatment strategies. The 2017/2019 WHO classification integrates further the grade of differentiation, based on morphology, and the Ki-67 grading, distinguishing grade 1, 2 and 3 well-differentiated neuroendocrine tumors from poorly-differentiated neuroendocrine carcinomas. The clear distinction between poorly-differentiated neuroendocrine carcinomas and well-differentiated neuroendocrine tumors is emphasized and the overall terminology neuroendocrine neoplasms is introduced (Table 2). In addition, a site-specific staging system is introduced. Long-term follow-up indicates that NETs as a category are malignant. This grading and staging system formally recognizes the malignant potential of NETs.

These historical changes in terminology and classification were absolutely necessary and are the consequence of a better understanding of the different nature of these rare tumors, by joining forces internationally. However, these frequent changes make it very difficult to exchange data or perform retrospective analyses – the work on the epidemiology of appendiceal and rectal NEN in Belgium for instance illustrates the need for reclassification, even for data gathered in the last ten years (6,7).

Reporting of neuroendocrine neoplasms

Since neuroendocrine neoplasms are rare tumors, registration of patient data in national and multinational registries is recommended. Indeed, this will facilitate multicenter studies on the epidemiology, and efficacy and safety of diagnostic and therapeutic strategies for neuroendocrine tumors as well as for neuroendocrine carcinomas. In order to make sound statements on epidemiology of the different subtypes but also on treatment-related outcomes, it is extremely important to use unequivocal terminology in pathology reports. This helps to clarify the exact classification and grading of the tumor over the years regardless of the used system. We hereby address the most important information pathology reports should include in order to enable investigators to retrieve the input needed (8).

We focus on:

1) Differentiation: morphology and immunohistochemistry
2) Grading: mitotic count and Ki-67 index
3) Staging, across pancreaticobiliary and gastrointestinal NENs.

Differentiation: morphology and immunohistochemistry

Well-differentiated neuroendocrine tumors (NET) are composed of rather uniform neoplastic cells, with organoid patterns, characterized by a nesting, trabecular, glandular, gyriform or pseudorosette arrangement of cells, round/oval nuclei with "salt and pepper" chromatin and low nuclear/cytoplasmic ratio. They present synapse-like vesicles as well as numerous neurosecretory-like dense-core granules responsible for intense and diffuse staining for the general neuroendocrine markers, synaptophysin and chromogranin. Nucleoli are usually inconspicuous. Mitoses are uncommon and necrosis is

Table 3. — **Immunohistochemical approach for the diagnosis of gastro-intestinal neuroendocrine neoplasms**

NET G1	NET G2	NET G3	NEC (SCNEC and LCNEC)
CGA** usually diffuse/intense		CGA** usually diffuse/intense	CGA** usually focal/faint
SYP **diffuse/intense		SYP **diffuse/intense	SYP **usually diffuse/intense or faint
Ki67** index < 3%	Ki67** index 3-20 %	Ki67** index > 20%	Ki67** index > 20%
		p53** usually weak nuclear staining (wild type)	p53** commonly overexpressed (strong, diffuse) or deleted (loss of nuclear staining)
		Rb** weak nuclear staining	Rb** occasionally loss of nuclear staining
			INSM-1** usually diffuse (nuclear)
SSTR2A* strong membranous staining		SSTR2A* strong membranous staining	SSTR2A* usually no membranous staining
	DAXX* and ATRX* loss of nuclear expression in 20-26% of PanNETs (G2/G3)		DAXX* and ATRX* preserved nuclear expression
CD56° diffuse/intense, but low specificity (not to be used as sole neuroendocrine marker)		CD56° low specificity	CD56° low specificity

** Strongly recommended, * Optional, ° Not recommended. SCNEC = Small cell neuroendocrine carcinoma, LCNEC = Large cell neuroendocrine carcinoma, CGA = Chromogranin A, SYP = Synaptophysin, SSTR2A = Somatostatin receptor 2A, Rb = Retinoblastoma, INSM-1 = Insulinoma-associated protein 1.

also generally absent. It should be mentioned that the immunohistochemical marker CD56 has low specificity and is not accepted to be used as sole neuroendocrine marker in tumors of the gastrointestinal tract. As there can be overlap in mitotic count and Ki-67 index between NET G3 and NEC (see further), immunohistochemistry for p53, Rb and SSTR2A is useful and recommended for differentiation (Table 3).

Poorly-differentiated neuroendocrine carcinomas (NEC) present as solid sheet-like or poorly formed organoid structures and are either of large cell (LCNEC) or small cell (SCNEC)-type (or mixed). SCNEC consist of small to medium sized cells with scant, finely granular cytoplasm, and hyperchromatic round to elongated nuclei with inconspicuous nucleoli and focal nuclear molding. LCNEC consist of medium to large sized cells with a moderate amount of cytoplasm, and round or polygonal nuclei with vesicular chromatin and prominent nucleoli. Necrosis is common and often abundant. Mitoses are plentiful and often atypical.

Neuroendocrine cells can be found in adenocarcinomas. A lesion is called a *mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)* when components of both a non-neuroendocrine tumor and a NEN can be found, each in at least 30% of the lesion (though this cut off is arbitrary and not evidence-based). MiNEN have been described in all organs of the digestive system, with highest frequency in the colon. The WHO 2010 classification recommended the term mixed adenoneuroendocrine carcinoma (MANEC) for such tumors. However, this term does not adequately cover the heterogeneity of possible combinations of neuroendocrine (well-differentiated or poorly-differentiated) and non-neuroendocrine (adenocarcinoma, squamous cell carcinoma or adenoma for example) phenotypes. The different components of MiNEN should be reported and graded individually. MiNEN can be stratified in categories according to the grade of malignancy of each component: low-grade MiNENs (adenoma and a WD-NET, called MANETs), high-grade MiNENs, (NEC with adenocarcinoma, called MANEC or squamous carcinoma in the esophagus or anal canal) and intermediate-grade neoplasms (composed of adenocarcinoma and NET). In general, the most aggressive cell population drives clinical behavior and thus should be considered for therapeutic strategy.

INSM1 is a useful marker of neuroendocrine differentiation in gastrointestinal neuroendocrine carcinomas and mixed neuroendocrine neoplasms. Compared with traditional neuroendocrine markers, INSM1 is less sensitive but more specific (8)

SSTR2A (somatostatin receptor 2A) expression is a feature of well-differentiated neuroendocrine tumors and has been suggested to be not only a diagnostic marker but also a predictive marker for treatment with peptide receptor radionucleide therapy (PRRT) and somatostatine analogues (SSA). However, its additional value compared to somatostatin receptor scintigraphy still needs further investigation, and more objective standardization of immunoreactivity is required before SSTR2A expression can be used as a predictive marker in clinical routine (9,10,11).

Pancreatic NET may show loss of immunohistochemical expression of DAXX or ATRX, which correlates with inactivating mutations of the underlying genes, and is associated with an adverse outcome. It can be found in NET G3 but excludes NEC (12)

Gastric NETs are subdivided into three main types. Type 1 and 2 gastric NET are ECLomas driven by hypergastrinemia, most often due to autoimmune atrophic corpus gastritis (type 1), and rarely due to a Zollinger-

Ellison syndrome (type 2). Type 3 gastric NET are rare and sporadic NET, which develop in non-atrophic oxyntic mucosa with variable degrees of inflammation and tend to behave more aggressively. For correct classification and risk stratification, biopsies of gastric mucosa at distance of the NET(s) are mandatory in order to detect a possibly underlying atrophic corpus gastritis, as proposed recently by the European Neuroendocrine Tumor Society (ENETS) (13). The type of gastric NET (type 1, 2, or 3) should be specified in the pathology report.

Unlike NET of the appendix, which are of low-grade malignancy, goblet cell carcinoids are more aggressive neoplasms. Goblet cell carcinoid/carcinoma has been renamed goblet cell adenocarcinoma in the WHO 2019, because it is predominantly composed of mucin-secreting cells and only harbors a minor component of neuroendocrine cells. Although the molecular profile of goblet cell adenocarcinomas is distinctive both from neuroendocrine tumors of the appendix and from colorectal-type appendiceal adenocarcinomas, these tumors are staged according to the UICC system as appendiceal adenocarcinomas rather than as appendiceal NETs, because of their more-aggressive course (4,14).

The results of immunohistochemical markers used to demonstrate the neuroendocrine nature of the tumor should be included in the pathology report. Reporting of the percentage of synaptophysin and chromogranin expressing cells is recommended as this can be useful for the (re)classification of mixed tumors (MiNEN) in the future.

Grading: mitotic count and Ki-67-index

The grade of neuroendocrine tumors represents a major prognostic factor and is evaluated on the basis of the proliferative activity (Ki-67 proliferation index and mitotic count) evaluated on tumor sections. The 2017/2019 WHO classification distinguishes grade 1, 2 and 3 well-differentiated neuroendocrine tumors from poorly-differentiated neuroendocrine carcinomas. Although NET G3 appear to have a somewhat worse prognosis than NET G2, their behavior is still less aggressive than that of NEC. Gastro-intestinal NET G3 are less common than NET G3 in the pancreas.

Ki-67 is a nuclear protein playing a pivotal role in maintaining cell proliferation. It is expressed in the active phases of the cell cycle (G1/S1/G2/M phases). Final grade is based on which ever index (mitotic count or Ki-67 index) places the tumor in the highest category. Discordance between grade assessed by mitotic count and Ki-67 index is seen in about 30% of cases. Generally, however, when there is discordance, it is the Ki-67 proliferation index that indicates the higher grade (15). For this reason, we consider inclusion of the Ki-67 index in the pathology reports as absolutely mandatory for adequate classification.

In WHO 2017-2019, grade cut offs have been slightly modified between G1 and G2. G1 NET have a Ki-67 index of < 3% and a mitotic count of < 2/10 HPF, while G2 NET have a Ki-67 index of 3-20% and a mitotic count of 2-20/10HPF (Table 2) (4). The suggested number of cells which should be counted has changed over the years, from 2000 cells in the WHO 2010 to at least 500 cells (500-2000 cells) in areas of high nuclear labeling ("hot spots") in the WHO 2017-2019 (4). Furthermore, not all methods of evaluation of Ki-67 are equally reliable. " Manual counting of printed images" is suggested (16). "Eyeballing" is not recommended. Mitotic count is required in 50 HPFs (at least 40 fields) (at 40X magnification, HPF=0.2 mm^2) in areas of highest mitotic density - expressed per 2.0 mm^2.

Besides technical aspects, other possible limitations of Ki-67 index assessment are a consequence from the small quantity of tissue available, such as small biopsies and, even more so, in case of cytology samples. Several studies have focused on the comparison of grading using endoscopic ultrasound guided fine needle aspiration and surgical pathology in pancreatic NENs. Overall, agreement between cytology and definitive histologic examination was extremely variable in studies ranging from as low as 34% to close to 100%. Clinicians should be aware that while it is true that cytology may not be able to accurately predict Ki-67 proliferation index in the intermediate range (distinction between G1 from G2 WD-NETs), it is however reliable in identifying very proliferative tumors (17,18).

A pathology report should therefore mention the precise value of the Ki-67 index (and preferably mitotic rate), next to the differentiation grade (NET G1/G2/G3 or NEC). It should also be stated whether grading was performed on the primary tumor or on metastases and whether the specimen was a cytology sample, a tissue biopsy or a surgical resection.

Staging, across pancreaticobiliary and gastrointestinal NENs

Always mention the staging system used. The 2017 edition of the UICC/AJCC (TNM8) staging manual has specified site-specific TNM systems for well-differentiated gastroenteropancreatic NETs including gastric, duodenal, ampullary, jejunal/ileal, appendiceal, colonic/rectal and pancreatic NET. The use of this updated system should be standard in all pathology reports (19,20). NEC on the other hand should be classified according to criteria for classifying carcinomas of the respective sites.

Staging of esophageal, anal, gallbladder NET and NET of perihilar bile ducts and extrahepatic bile ducts follows the criteria for carcinoma of these organs. Staging of hepatic NET follows the criteria for intrahepatic bile duct carcinoma.

Size, deepest point of invasion and T category

It is necessary (for NET as well as for NEC) to always report **the exact dimensions (maximal diameter)** of

the primary tumor, as well as to specifically mention the **deepest level of invasion/local extension of the tumor** in addition to the currently corresponding T category.

Indeed, for the gastrointestinal (GI) tract (esophagus, stomach, duodenum, ileum/jejunum, colon/rectum, appendix and anal canal) the size of the tumor is not/the only parameter taken into account in several risk stratifications, but also the deepest level of invasion.

For NEN of the GI tract it should be reported whether there is invasion of the mucosa, submucosa, muscularis propria, subserosa/adventitia/non-peritonealized pericolic or perirectal tissue, perforation of the serosa/invasion of adjacent organs or structures. For NET of the ampulla, it should be specified whether the tumor infiltrates within the sphincter of Oddi, through the sphincter into the duodenal submucosa or muscularis propria, into the pancreas or peripancreatic adipose tissue, and for pancreatic NEN whether it invades the duodenum or bile duct or whether it perforates the serosa/invades into other organs or adjacent structures (19,20).

Site-specific staging systems were only recently introduced for gastro-intestinal NET and it is clear that they will be updated in the future as new information is gathered. Reporting of both the exact dimension of the tumor as well as the deepest level of invasion will allow adaptation of the T category in case of major changes in future editions of the TNM staging system.

The **number of primary tumors** should be stated - this is especially important for ileal NET. According to the TNM system the tumor with the highest T category should be classified and the multiplicity of the primary tumors at a single site or the number of tumors should be indicated as a suffix in parenthesis, e.g. T1(m) or T1 (3).

For appendiceal NET it is recommended to report the depth of extension into the mesoappendix (in mm).

R status

The R descriptor refers to the presence or absence of residual disease and in clinical practice the R-status is usually regarded as synonymous to the resection margin status. Margin assessment is based on combined macroscopic and microscopic measurement. The minimum distance of the tumor to the closest margin(s) should be measured and included in the pathology report.

N category

Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. The number of examined lymph nodes should be mentioned. There is no further substaging according to the number of affected lymph nodes for primary sites that have a site-specific NET TNM classification: we only differentiate between NX, N0 or N1.

For small intestinal NET it is recommended to report the size of the biggest lymph node metastasis (8).

For jejunal and ileal NET in addition specific attention needs to be paid to the presence/absence of mesenteric mass(es) larger than 2cm: if such mass(es) is present, the N category is by definition N2.

- *NX: Regional lymph nodes cannot be assessed*
- *N0: No regional lymph node metastasis*
- *N1: Any*

  Exception: Jejunum/ileum
  - *N1: <12 and no mesenteric mass(es) > 2cm*
  - *N2: ≥12 and/or mesenteric mass(es) > 2cm*

For esophageal and anal neuroendocrine neoplasms, as well as for hepatic NET and NET of the perihilar or extrahepatic bile ducts or the gallbladder, where staging follows the rules of the staging systems for adenocarcinoma, obviously there is no specific staging system for N status either.

Several studies identified lymph node ratio as a significant predictor of recurrence after resection (21, 22); therefore, it is advised to include this ratio in the pathology report.

Table 4. — **Minimal requirements of a NEN pathology report**

Anatomic site of the tumor
Differentiation and WHO tumor type WD NET, NEC (large/small cell-type), MiNEN (histotype of NE and non-NE components)
Tumor grade (< 3% for G1, 3-20% G2, > 20% G3) for NET
Type for gastric NET (type 1, 2 or 3)
Ki-67 index as precise value (%)
Size (maximal diameter)
Depth of invasion/local extension of the tumor
Lympho-vascular invasion (present/absent)
Perineural invasion (present/absent)
Lymph node status (number of evaluated nodes, number of positive nodes)
R status and description of margins (distance to the closest margin)
Immunohistochemical markers used (minimum synaptophysin and chromogranin A)
pTNM stage (UICC) with indication of the edition used

Perineural and lymphovascular invasion

As for adenocarcinoma's, perineural and lymphovascular should be mentioned, because these features are often included in risk stratification when decisions on the extension of surgery have to be made in localized disease.

- Perineural invasion: Pn0 or Pn1
- Lymphatic invasion: L0 or L1
- Vascular invasion: V0 or V1 (microscopic) or V2 (macroscopic)

In practice it is not always possible to distinguish between invasion in lymph vessel or small blood vessel, in this case, we propose to use the designation LV0, LV1 or LV2.

Metastasis

As for adenocarcinoma's, pM can only be used if a biopsy of a metastatic site was taken.

- M0: No distant metastasis
- M1a Hepatic only
- M1b: Extrahepatic only
- M1c: Hepatic and extrahepatic

Conclusion

As minimal requirements, a pathology report of a pancreaticobiliary and gastrointestinal NEN should include anatomic site of the tumor, differentiation and WHO tumor type (WD NET, NEC (large/small cell-type), MiNEN (histotype of NE and non-NE components), tumor grade (< 3% for G1, 3-20% G2, > 20% G3) for NET and Ki-67 index as precise value (%), the type for gastric NET (type 1, 2 or 3), size (maximal diameter), depth of invasion, lympho-vascular invasion (present/absent), perineural invasion (present/absent), lymph node status (number of evaluated nodes, number of positive nodes), R status and description of margins (distance to the closest margin), immunohistochemical markers used, pTNM stage (AJCC/UICC) with indication of the edition used (Table 4).

It needs to be emphasized that despite the use of uniform terminology, there are important organ-specific differences among NEN in terms of hormonal function, clinical presentation, prognosis, morphology, and genomics; the current WHO classification system is intended to standardize the approach to diagnosis and grading, but not to replace the key additional information to be included in pathological diagnosis reflecting the unique features of each NEN (4, 23).

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