

## REVIEW

## Aspects regarding nomenclature, classification and pathology of neuroendocrine neoplasms of the digestive system – a review

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### Abstract

Neuroendocrine neoplasms (NENs) of the digestive system are composed of cells with a neuroendocrine phenotype. These tumors produce and secrete peptide hormones and biogenic amines and they are called *neuroendocrine neoplasms* because of the marker proteins that they share with the neural cell system. The classification and nomenclature used to designate NENs have undergone changes over the past decades due to the accumulation of evidence related to the biological characteristics and their evolution. The *European Neuroendocrine Tumor Society* (ENETS) proposed a classification system based on the tumor grading and staging according to their localization. The latest internationally recognized NEN classification was published by the *World Health Organization* (WHO) in 2010. In accordance with the 2010 WHO criteria, the determination of the NEN malignancy potential is based on grading, depending on the mitotic activity and the Ki67 proliferation index, as well as on the tumor TNM stage. It is worth emphasizing that the terms *neuroendocrine tumor* (NET) and *neuroendocrine carcinoma* (NEC), without reference to grading or differentiation, are inadequate for prognostic assessment or the therapy determination, being inappropriate in pathology reports. The functional status of the tumor is based on the clinical findings but not on the pathological data or immunohistochemically profile. Despite the inability to establish a single system of sites, these are common features to establish the basis of most systems, documentation of these features allowing for greater reliability in the pathology reporting of these neoplasms.

**Keywords:** neuroendocrine neoplasms, pathology, classification, nomenclature, staging, grading.

### ☒ Definitions

The term *neuroendocrine tumor* (NET) is used to describe a heterogeneous group of neoplasms formed by cells embodying two phenotypes: endocrine and neural.

The neuroendocrine phenotype is present in a series of cells that secrete amines and hormones under the name of *diffuse endocrine system*, a concept introduced by Feyrter in 1938 and later developed by Pearse in 1969, which features the amine precursor uptake and decarboxylation (APUD) diffuse system.

The diffuse neuroendocrine system associated with the gastroenteropancreatic tract consists of at least 14 types of cells showing autocrine, paracrine and local neuro-modulatory effects, which result from the differentiation of progenitor cells.

### ☒ Normal neuroendocrine cells

There are three categories of neuroendocrine cells that can be morphologically identified by routine Hematoxylin–Eosin staining but only one type, namely enterochromaffin cells (ECs), can be recognized exclusively histologically, without the need for immunohistochemically tests or microscopic examination of cytoplasmic secretory granules.

Three cell types are described: ECs, open neuroendocrine cells and closed neuroendocrine cells [1].

### Enterochromaffin cells

ECs are the most common neuroendocrine cells in the gastrointestinal tract and produce serotonin, a hormone responsible for the clinical manifestations of the carcinoid syndrome and P-subtype (produced by a subunit of ECs located in the jejunum and ileum). They constitute the majority of neuroendocrine cells in the small intestine mucosa (except the duodenum), appendix and colon, and may be seen as dispersed in the stomach and rectum. ECs are conical or polygonal in shape and small. The cytoplasm is directed towards the basement membrane, where it drains the secretion, is finely granular with eosinophilic granules. The round-oval nucleus is located to the crypt lumen and shows a fine chromatin, with no observable nucleoli.

### “Open” neuroendocrine cells

“Open” neuroendocrine cells contain the cytoplasm that communicates with the crypt lumen. These are G-cells, D-cells (somatostatin secreting cells) and L-cells (enteroglucagon-secreting cells). G- and D-cells are found

predominantly in the antrum and duodenum, whereas the L-cells are located in the rectum and ileum terminal, but also at the appendix level. The cells are small, oval, with an EC-like nucleus and clear cytoplasm, and they can easily be mistaken for intraepithelial lymphocytes.

### “Closed” neuroendocrine cells

“Closed” neuroendocrine cells have a histological appearance similar to open neuroendocrine cells, but they do not communicate with the crypt lumen, reacting to circulating hormones. The prototype is represented by enterochromaffin-like cells (ELCs) in the gastric parietal mucosa, which secretes histamine when stimulated by gastrin, causing gastric acid production.

In order to accurately detect the exact type of endocrine cells according to their secretion, immunohistochemistry is highly useful, identifying the secretion of many hormones including serotonin (ECs), gastrin (G-cells), somatostatin (D-cells), enteroglucagon (L-cells) and substance P. We mention that the immunohistochemical (IHC) expression of hormones does not necessarily correlate with the presence of a functional tumor.

Electron microscopy is rarely required for diagnostic purposes, but it may be used in the case of liver metastases of small-cell poor tumors. The identification of neurosecretory granules is a strong argument in favor of neuroendocrine differentiation [1, 2].

The system was formerly called APUD, a term currently considered to be outdated [3].

Some of the neuroendocrine cells are of neuroectodermal origin (paraganglion cells, olfactory cells, Merkel cells, thyroid C-cells, parathyroid cells), and others have on-site origin, such as neuroendocrine cells in the intestine, pancreas, bronchi and urogenital tract. The former are non-epithelial and do not have positive IHC expression for cytokeratins.

Not all types of neuroendocrine cells give rise to NETs, for example, NETs are not related to cholecystokinin- and secretin-producing cells.

### ☞ Neuroendocrine tumor

NET is a well differentiated neuroendocrine neoplasm (NEN), G1 or G2 according to the *World Health Organization* (WHO) classification of 2010, composed of cells similar to the normal intestinal endocrine ones and expressing general IHC markers of neuroendocrine differentiation (intense and diffuse positive expression of chromogranin A and synaptophysin) and hormone-specific tumor localization. Tumor endocrine cells display mild or moderate nuclear atypia and a small number of mitoses [ $<20$  mitoses/10 high-power fields (HPFs)]. This entity includes neoplasms called *carcinoids* in the previous classifications [4].

### ☞ Neuroendocrine carcinoma

The neuroendocrine carcinoma (NEC) is a poorly differentiated NEN composed of small tumor cells or large cells, which form NET-like organoid structures. The cells express diffusely neuroendocrine differentiation IHC markers (diffuse positive synaptophysin expression and weak expression of chromogranin A) and show

marked nuclear atypia, multifocal necrosis and a large number of mitoses ( $>20$  mitoses/10 HPFs) [5].

### ☞ Mixed adenoneuroendocrine carcinoma

The mixed adenoneuroendocrine carcinoma (MANEC) is a malignant neoplasm in which two distinct morphological components can be identified, each present in a proportion higher than 30% of the tumor surface area. The presence of several immunohistochemically identifiable dissociated neuroendocrine cells is not sufficient for the tumor classification in this category. The presence of a squamous component is rare [5].

Neuroendocrine system cells, as well as tumors originating in them, share common antigens with nervous system elements, such as neuron-specific enolase (NSE), protein gene product 9.5 (PGP9.5), cluster of differentiation 56 (CD56), synaptophysin and chromosomes A, B and C. The expression of these common molecules is a strong argument for using the term *neuroendocrine neoplasm*.

A number of scholars consider stem cells to be at the root of NENs, differentiating some primitive neuroendocrine precursor cells that can give rise to poorly differentiated NECs, or that can be further differentiated into programmed neuroendocrine precursor cells from which well differentiated NETs arise [6, 7].

In 1907, Oberndorfer noticed some small tumors in the small intestine, which he labeled *Karzinoid*, and for a long time the name of carcinoid tumors has been preserved for these types of neoplasia. The term *carcinoid* is still used by some authors as a synonym of well-differentiated NETs [8].

### ☞ Functional/nonfunctional neuroendocrine neoplasms

The hyperproduction of hormones at the level of NENs may result in the presence of a clinical syndrome, in which case the NEN will be called *functional NEN* or *NEN syndrome*.

The carcinoid syndrome, present in 8–10% of NET-bearing patients, is generated by these tumors release of vasoactive substances, mainly serotonin, but also other such substances such as histamine and substance P, in the systemic circulation.

Due to serotonin inactivation largely in the liver, where it reaches through portal circulation, clinical manifestations are obvious especially in the presence of liver metastases or in extradigestive localizations (ovarian, bronchial, etc.).

The secretion of hormones by NENs is assessed immunohistochemically, nevertheless, the classification is not exclusively based on immunophenotypes, but in correlation with the functional status of the tumor. Thus, a tumor will be named after the hormone produced, using predominantly the suffix “-oma” (e.g., insulinoma) only if there is a clinical syndrome determined by it [9].

In the absence of clinical manifestations, in the histopathological report the term “neuroendocrine tumor of ...” is accepted, depending on the immunophenotype of the neoplasm.

Frequently, small-cell populations that produce other peptides with hormonal effects are identified in the tumor.

It is possible that NEN metastases may express other hormones than the primary tumor [10].

### ☞ Classification and nomenclature of neuroendocrine neoplasms of the digestive system

The classification and nomenclature used to designate NENs have undergone changes over the past decades due to the collection of evidence related to biological characteristics and their evolution [8, 11–13].

The latest internationally recognized classification was published by the *WHO* in 2010 [14] (Table 1).

**Table 1 – WHO 2000 compared to WHO 2010 classification of tumors of the digestive system (from Bosman et al., 2010) [11]**

WHO 2000	WHO 2010
Well-differentiated endocrine tumor	NET G1 (carcinoid)
Well-differentiated endocrine carcinoma	NET G2
Low differentiated endocrine carcinoma/small-cell carcinoma	NEC (large-cell or small-cell) G3
Mixed exocrine-endocrine carcinoma	Mixed adenoneuroendocrine carcinoma
Tumor-like lesions	Hyperplastic and preneoplastic lesions

WHO: World Health Organization; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

Prior to this, the *European Society for Neuroendocrine Tumors* (*ENETS*) proposed two complementary tools to classify them: a classification according to the tumor grading and staging according to localization [15, 16].

*ENETS* highlighted a number of key concepts related to the way NENs are considered today:

- NEN heterogeneity (different primitive localizations);
- Tumor differentiation;
- Malignancy (long-term monitoring indicates that the NEN, as a family of tumors, is malignant).

For NEN grading, morphological criteria (specific to NEN localization) and proliferation fraction assessment (according to *ENETS*) are used (Table 2).

**Table 2 – Grading for digestive NETs (from Couvelard, 2015) [11]**

Grade of differentiation	Criteria
G1	<2 mitoses/10 HPFs and/or ≤2% Ki67 index
G2	2–20 mitoses/10 HPFs and/or 3–20% Ki67 index
G3	>20 mitoses/10 HPFs and/or >20% Ki67 index

NET: Neuroendocrine tumors; HPFs: High power fields.

In this grading system it is necessary to perform a mitotic count in at least 50 HPFs (2 mm<sup>2</sup>), and to estimate the proliferation index, and the percentage of positive cells out of the 500–2000 cells evaluated in the hot spot area has to be used. If the mitotic count and the proliferation index indicate different grades, the lesser grade of differentiation will be taken into consideration [5, 17].

Well and intermediate differentiated tumors (G1 and G2) may show malignant potential by local invasion and/or lymph nodes or distant metastases (Table 3).

**Table 3 – Pathology reporting of NETs: essential elements for accurate diagnosis, classification, and staging (from Klimstra, 2013) [17]**

NEN	NET	NEC
Grade of differentiation	Well differentiated (G1, G2)	Poorly differentiated (G3)
Hormonal expression (specific local hormones)	Present	Absent
Hormonal syndromes (functional tumors)	Present	Absent
Genetic	Miscellanea	<i>p53</i> and <i>RB</i> genes mutations
Associated with smoking, viral infections	Absent	Present

NEN: Neuroendocrine neoplasm; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; RB: Retinoblastoma.

Cyto-morphological modifications of aggressive behavior (cellular atypia, higher mitotic index, vascular invasion) do not determine the classification of a tumor as a malignancy, but as a “well differentiated tumor with uncertain behavior” in the absence of local or remote dissemination [17, 18].

In accordance with the *WHO* 2010 criteria, the determination of malignant potential groups is based on both grading, mitotic and Ki67 activity, and TNM tumor status [5, 17].

To improve prognostic relevance, *ENETS* recommends the use of the grading system in conjunction with a staging system specific to each gastroenteropancreatic localization [17, 19].

Unlike previous classifications, this identification of the tumor stage also applies to NEN metastases. Both grading and TMN staging specific to localization are required to define the malignant potential [18, 19].

A staging system for digestive tract NEN has been proposed through modifying or accepting TMN stages corresponding to carcinomas with the same localization [17, 19].

There are some significant differences between the European NEN staging system adopted in 2006 (*ENETS*) and the one adopted by the *American Joint Committee on Cancer* (*AJCC*) in 2009 for the stomach and appendix and the absence of a specific incidence of mixed carcinomas, depending on the exocrine or endocrine component [19].

Staging is based primarily on criteria such as: tumor size, invasion of the muscularis mucosae, serosa and adjacent structures [18–20].

### ☞ Histological patterns of neuroendocrine neoplasms

#### Type A (island or nest)

This histological pattern is particularly characteristic of NETs with ECs. The tumor is composed of nests, islands or stretches in which cells are organized compactly, evenly, are monomorphic and show no mitotic activity. There is only a minimal fibro-vascular tissue between the cellular cords. Sometimes, there is a vague dissection in the peripheral palisades of neuroendocrine cell nuclei. The histological type A indicates a primitive localization of a NET in the digestive tract of embryonic origin in the middle intestine (duodenum II, III and IV, jejunum, ileum,

appendix, ascending and transverse colon) and it is particularly characteristic of ileal NETs.

### Type B (trabecula)

Type B prevails in L-cells, most commonly encountered in the rectum. Tumor cells form trabecular or long rods, usually a cell thick, which may be curvilinear, similar to garlands, or short, like an infiltrative mammary lobular carcinoma. The stroma is very small, there are no atypia or mitoses, and necrosis is absent or minimal. The presence of the pure B-type is specific to the NET with gastrointestinal localization deriving from the caudal intestine (the distal third of the transverse colon, descending colon, sigmoid and rectum).

### Type C (acinar)

NET cells of the histological type C form adenoidal lumen structures that sometimes contain secretions and bodies of psammoma, with no identification of true glands. The cells are polygonal, small, and the nuclei are not directed towards the basement membrane. The acinar type is commonly found in somatostatin-producing duodenal NETs. However, the exclusive presence of type C does not apply to all gastrointestinal sites derived from the anterior intestine, and a combination of histological patterns is customarily noticed in the stomach.

### Type D (poorly differentiated)

In this histological type, tumor cells exhibit neuroendocrine nuclear features but with a high nuclear/cytoplasm ratio and a disorganized, trabecular pattern and in poorly defined nests. This histopathological aspect indicates malignant behavior, and it can be observed focally in colonic NETs, alongside types A and B of neuroendocrine patterns [1, 2].

## Essential minimum data in the histopathology report recommended by the WHO

For the histopathology report, WHO recommended the following essential minimum data [13, 16]:

#### Macroscopic data:

- Exact localization of the tumor;
- Exact size of the tumor;
- Distance to the edge of the resection.

#### Microscopic data:

- Mitotic count per 10 HPFs;
- Number of evaluated fields;
- Ki67 proliferation index.

#### Mandatory elements for the final diagnosis:

- Tumor classification (TNM or CNE);
- Tumor grade (G1, G2 or G3);
- TNM staging specific to localization (for tumor resection).

#### Optional histopathological data:

- Immunohistochemically detectable endocrine profile (does not necessarily correlate with the presence of a clinical syndrome of excessive hormone production by the tumor).

## Immunohistochemistry of neuroendocrine neoplasms

Neuroendocrine cells can be identified immunohistochemically by membrane or cytoplasmic markers.

Somatostatin receptors (SSTRs) and CD56 show a membrane reaction.

NSE and PGP9.5 may be positive for cytoplasm.

The cytoplasm of neuroendocrine cells may contain two types of secretory vesicles: synaptic-like small vesicles evidenced by synaptophysin, and larger vesicles with a positive IHC reaction to chromogranin A and other markers such as vesicular monoamine transporter (VMAT).

The positive expression of common markers with cells of nerve origin (synaptophysin, CD56, PGP9.5 and NSE) is an argument for using the term *neuroendocrine neoplasm* [21–23].

For the accurate determination of neuroendocrine differentiation it is recommended to use a panel of at least two antibodies that include synaptophysin and chromogranin A, considered to be general neuroendocrine markers [24].

NETs (G1, G2) are usually diffuse and strongly positive in the two markers, whereas NECs (G3) usually express diffuse synaptophysin and express poorly, focally or negatively for chromogranin A [22, 23].

The production of hormones by the tumor can be studied immunohistochemically, but tissue expression does not necessarily correlate with the presence of a clinical syndrome determined by hormonal overproduction, and thus of a functional tumor. Admittedly, the name of a tumor based solely on the hormone immunophenotype using the suffix “-oma” (insulinoma, glucagon) is not correct.

Typically, NETs predominantly contain a type of hormone (e.g., gastrin in gastrinomas, somatostatin in somatostatinomas, etc.) that can cause clinical manifestations, but there are usually minor cell populations expressing other hormones, such as cholecystokinin, secretin, pancreatic polypeptide (PP), adrenocorticotropic hormone (ACTH), substance P, neurotensin, motilin [25, 26].

The metastasis of NENs may have a hormonal immunophenotype different from the primary tumor.

Most NETs with gastrointestinal localization of embryonic origin in the mid-intestine (distal, ileum, colon, jejunum) are positive for caudal-type homeobox 2 (CDX2), while most rectal NETs are negative. NECs may have nuclear IHC reaction for p53 [27–29].

### Proliferation index

To assess the grade of tumor differentiation, it is necessary to evaluate the mitotic count and/or the Ki67 proliferation index according to the *ENETS* scheme. While the mitotic count is difficult to standardize, the nuclear expression of Ki67 is more objective. Thus, tumors displaying Ki67  $\leq 2\%$  proliferation index and/or mitotic count  $< 2$  mitoses/10 HPFs correspond to G1 grade, those with a Ki67 index ranging between 3% and 20% and/or 2–20 mitoses/10 HPFs correspond to G2 grade and Ki67 index  $> 20\%$  and/or mitotic count  $> 20$  mitoses/10 HPFs correspond to G3 grade.

This classification according to the tumor grade has a prognostic value and correlates with the tumor size and its metastasis capacity [3, 30].

### Determination of primitive origin of NEN metastases

NENs most commonly metastasize to the liver, lungs and bones. Rare localizations of NEN metastases are cerebral, cardiac, ovarian, mammary, thyroid, pancreatic, splenic, renal, dermal, suprarenal, orbital and pituitary.

The IHC markers thyroid transcription factor 1 (TTF1) and CDX2 are very useful to assess the primary origin of a NEN. TTF1 is positive in over 90% of typical and atypical pulmonary carcinoids as well as in large-cell pulmonary NECs, and it is rarely expressed in NETs with extra-pulmonary primitive localization [31, 32].

In contrast, extra-pulmonary small-cell carcinomas are positive for TTF1 (in 40–80% of cases), making the differential diagnosis difficult [33].

CDX2 is a marker specific to digestive differentiation, many of the gastrointestinal NENs being positive, especially those with primitive hernia, ileal and colonic localization [33, 34].

Pancreatic NENs show pancreatic and duodenal homeobox 1 (PDX1), insulin gene enhancer protein (ISL1) positivity, as well as for neuroendocrine secretory protein 55 (NESP55), a member of the chromogranin family [35].

CDX2, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) may also be positive in NETs of pancreatic origin [36].

### ⊞ Molecular pathology

Unlike adenocarcinomas, NEN pathogenesis has not demonstrated systematic progression through successive mutations towards malignancy. Instead, NENs exhibit specific biological behavior depending on their localization and embryological origin.

NENs of the digestive tract derived from the former primitive intestine frequently present chromosome 11q13 changes in the *menin* 1 (*MEN1*) gene locus encoding the protein called *menin* [37].

Anomalies of this gene are responsible for the occurrence of *MEN1* syndrome, where there is a combination of multiple endocrine tumors in the pituitary gland, parathyroid gland, pancreas, and stomach [38].

Other genetic modifications are described as loss of heterozygosity (LOH) 11q13, overexpression of Erb-b2 receptor tyrosine kinase 2 (ERBB2) on chromosome 17q21, loss of B-cell lymphoma 2 (*BCL2*) expression (in type 1 gastric NET) and others [37, 38].

NENs of the intestinal tract derived from the primitive mid-intestine present anomalies of the chromosome 18q, and losses of 11q, 16q. LOH at chromosome 18 was identified in 86% of ileum NETs. Other genes involved in the NEN pathogenesis of the mid-intestinal tract are deleted in colorectal carcinoma (*DCC*), deleted in pancreatic carcinoma locus 4 (*DPC4/SMAD4*), cadherin 1 (*CDH1*), *CTCF* and *MYC* (c-myc) [39, 40].

NENs with intestine localization derived from the caudal intestinal tract present totally different genetic changes.

Epidermal growth factor receptor (EGFR), a member of the human epidermal growth factor receptor 2 (HER2) transmembrane signaling protein family, is overexpressed in NEN and in the presence of metastases [41].

An abnormal expression of transforming growth factor-beta (TGF- $\beta$ ) has also been observed. Another frequent change is represented by gene silencing through methylation. Also,  $\beta$ -catenin is overexpressed in 79% of the digestive NENs with this localization [41].

In addition to the multiple endocrine neoplasia (MEN) syndrome, other genetic syndromes associated with NENs are neurofibromatosis type 1 (NF1) (ampullary and periampullary NET), von Hippel–Lindau (VHL) disease (functional duodenal NET producing somatostatin and pancreatic NET), and Bourneville tuberous sclerosis [41].

### Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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