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Review

CLASSIFICATION OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

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Summary

Gastroenteropancreatic neuroendocrine tumors are a heterogeneous group of tumors. There are several classification systems, and all of them have been validated.The article aims to summarize the existing classification systems of gastroenteropancreatic neuroendocrine tumors.A critical evaluation was based on the data available from existing studies.The classification of the European neuroendocrine tumor society is the one with the clinical benefits.The lack of unified classification systems creates incomplete epidemiologic data, leading to confusion among pathologists and clinicians.

Keywords: gastroenteropancreatic neuroendocrine tumors, classification

Introduction

The concept of neuroendocrine cells has evolved, along with the definition of neuroendocrine tumor. The term "carcinoid" was first introduced by Siegfried Oberndorfer in 1907 [1]. Neuroendocrine carcinomas are defined as a biologically distinct group of well-differentiated neuroendocrine tumors. This, in turn, necessitated the introduction of two terms: neuroendocrine tumor and neuroendocrine carcinoma. In pathological practice, proliferation is the main criterion for distinguishing less aggressive tumors from aggressive carcinomas. In Europe, the Ki-67 index is used more frequently, while in the United States, the mitotic count is used instead to determine the grade of proliferation [2].

Classifications of NETs

In 2009, an expert group of the ENETS offered guidelines and recommendations for the pathological assessment, diagnosis, and classification of neuroendocrine neoplasms. The group created an international register of NETs. In the following years, using the accumulated knowledge of their biology, many diagnostic and

classification changes were made and reflected in the WHO 2010, 2015, and 2017 classifications.

The WHO 2000 classification system

uses the generic name of neuroendocrine tumors and classifies lesions based on their size, rate of cell proliferation, localization, differentiation, and hormone production. The WHO initial classifications (Gastrointestinal NETs, 2000 and Pancreatic NETs, 2004) combined data on tumor size and information for classification needs (mitosis count/Ki-67 proliferative index) into a new prognostic group with a different name.

TNM systems for the classification for the classification of NETs

Other widely used and recognized TNM systems for the classification of NETs are those proposed by the American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS). Both systems are anatomically specific. The system the AJCC proposed includes neuroendocrine tumors of all anatomical regions, while the ENETS recommendations are limited to the TNM classification for gastroenteropancreatic NETs only (Table 1).

The general guidelines for the diagnosis of neuroendocrine tumors of the North American Neuroendocrine Tumor Society (NANETS) suggest the objectives for the initial classification of NETs to include primary tumor identification, disease grade assessment, treatment planning, and recommendations for a diagnostic imaging examination performed at the very beginning of tumor detection.

There are currently insufficient data to validate any of the classification systems. Therefore, it is recommended to indicate the degree of tumor dissemination in the primary site and organs with metastasis and mention the TNM system used for staging in the histological result [3].

Williams and Sandler 1963 Classification (Embryonic classification)

Sandler developed the first classification of neuroendocrine neoplasms in 1968. It is mechanical, based on embryonic development. Three subsets are recognized based on their original subject of derivation:

- Foregut carcinoids: respiratory system, stomach, duodenum, proximal jejunum, and pancreas
- Midgut carcinoids: distal jejunum, ileum, and right colon
- Hindgut carcinoids: transverse colon, left colon, and rectum.

Anatomical classification

- Pituitary gland: chromophobic, anterior pituitary NET
- Thyroid gland: neuroendocrine thyroid tumors and thyroid medullary carcinoma (TMC)
- Parathyroid tumors
- Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
- Liver and gallbladder;
- Cervix;
- Urinary bladder;
- Prostate;
- Catecholamine-secreting tumors - tumors of

Table 1. The TNM-classification of pancreatic neuroendocrine tumors (ENETS)

T	Primary tumor
Tx	The primary tumor cannot be assessed
T0	There is no evidence of a primary tumor
T1	Tumor <2 cm in size, confined to the pancreas
T2	Tumor 2–4 cm in size, limited to the pancreas
T3	Tumor >4 cm in size, confined to the pancreas or invading the duodenum or biliary duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or a large vessel wall (*truncus caeliacus* or *arteria mesenterica superior*)

* (m) is added for each type of T if multiple tumors are present.

the adrenal glands and pheochromocytoma;
- Merkel cell tumors

Hereditary conditions

- Type 1 multiple endocrine neoplasias (MEN1)
- Type 2 multiple endocrine neoplasias (MEN2)
- Von Hippel-Lindau disease (VHL)
- Type 1 neurofibromatosis
- Tuberculous sclerosis

The UICC/AJCC classification system

The seventh edition of the UICC/AJCC phasing-in system recommends that GEP-NETs have an additional stage depending on the site of origin. In contrast, neuroendocrine carcinomas (large- and small-cell carcinomas) and all pancreatic carcinomas should be staged as conventional carcinomas [4-6].

The clinical classification based on the AJCC recommendations depends on the anatomical localization and pathological condition obtained by endoscopic biopsy, percutaneous biopsy, fine-needle aspiration, surgical examination, and examination of the primary surgically resected tumors lymph nodes, and distant metastases. In 2010, the AJCC Cancer Staging Manual introduced a three-grade scale to determine tumor differentiation. (Table 2)

Histological classification

J. Suga and Y. Yakima developed the first morphological classification in 1971 [7-9]. In 1970, immunohistochemistry was introduced to determine the neuroendocrine nature of tumors. In 2018, the new requirements and recommendations for pathomorphological diagnosis, histological grading, and staging of NETs included a change in the criteria for the IHC assessment of Ki-67 index in NETs G1-G2 (<3% and≥3-20%, respectively) and the introduction of a new classification category – highly differentiated NET G3 [10,11].

The ENETS classification system

The ENETS system only applies to gastroenteropancreatic NETs. According to the WHO 2010 classification, gastroenteropancreatic neuroendocrine tumors are classified into three subsets based on the mitotic count or Ki-67 index:

- G1 (mitotic count <2/10 HPF and/or Ki-67 index <3%),
- G2 (mitotic count 2-20/10 HPF and/or Ki-67 index 3-20%),

Table 2. Pathoanatomical determination of the degree of differentiation by proliferative grading

Histological degree of differentiation	Mitotic count (per 10 HPF)*	Ki-67 index (%)**/***
G 1	<2	<2
G 2	2 - 20	3 - 20
G 3	>20	>20

* Total number of mitoses counted in 10 fields at microscopic magnification x 40 (= 2 mm2);
** % of counted 500/2,000 tumor cells in the fields with maximum nuclear staining (3+);
*** In appendix tumors, there are no recognized criteria for assessing the Ki-67 index.

Table 3. Histological classification and determination of the degree of differentiation by the mitotic count and/or Ki-67-index in gastroenteropancreatic neuroendocrine neoplasms - AJCC 2017, ENETS 2017, WHO 2017 [12,13,14]

Histological degree of differentiation and classification	Mitotic count*	Ki-67 index (%)**
Highly differentiated N**ET G1**	<2	<3
Highly differentiated N**ET G2**	2-20	3-20
Highly differentiated N**ET G3**	>20	>20
Neuroendocrine carcinoma G3	>20	>20

* Total number of mitoses counted in at least 10 fields at microscopic magnification x 40 (= mm2) ** % of 500/2,000 positive/negative tumor cells counted in fields with a predominant number of stained nuclei (the so-called „high power fields, HPF“)

- G3 (mitotic count >20/10 HPF and/or Ki-67 index >20%).

G1 and G2 neoplasms have well-differentiated morphology and are referred to as G1 or G2 neuroendocrine tumors, while G3 tumours are considered poorly differentiated and are referred to as neuroendocrine carcinomas. G3 carcinomas, in turn, are subdivided into small cell and large cell carcinomas [15-17].

The histological grading and classification of NETs based on the Ki-67 index, also recommended by the WHO 2010, were also refined. According to current requirements, NETs with Ki-67 <3% are determined as G1, and those with Ki-67 3-20% - as G2 tumors. Studies have shown that the group of neuroendocrine neoplasms is not homogeneous in terms of clinical response to chemotherapy [18,19,20]. Therefore, the WHO 2017 classification introduced the new G3 category of neuroendocrine tumors. By 2018, the G3 category had been subclassified into highly differentiated NET G3 (index >20% to 40-55%) and NET G3 (index >20% or >55%). [21, 22]

The classification of neuroendocrine neoplasms has constantly been evolving since the introduction of their concept in 1996 (Table 4).

WHO 2010 classification

The classification system introduced after the ENETS meetings is well-recognized and has a proven clinical benefit for prognosis. With the consensus on the WHO 2010 classification, the neuroendocrine concept was adopted for the first time in Europe and the United States [23-25].

Classification according to the functionality of NETs

The presence of clinical symptoms and

Table 4. Classification scheme for histological assessment of gastroenteropancreatic neuroendocrine tumors

WHO 1980	WHO 2000	WHO 2010
Carcinoid	Highly differentiated endocrine tumor	Neuroendocrine tumor = G1 (carcinoid)
	Highly differentiated endocrine tumor	Neuroendocrine tumor = G2
	Poorly differentiated endocrine carcinoma (small cell carcinoma)	Neuroendocrine carcinoma (large-cell or small-cell) = G3
Mucocarcinoid Mixed form of carcinoid and adenocarcinoma	Mixed exocrine-endocrine carcinoma	Mixed adenoneuroendocrine carcinoma (the neuroendocrine component is up to 30% of the tumor volume)
Pseudotumor lesions	Tumor-like lesions	Hyperplastic and preneoplastic lesions

Table 5. The WHO 2010 NET classification

Well-differentiated neuroendocrine tumors	Ki-67 index	Mitotic count
1. Neuroendocrine tumor G1	3%	2/10 HPF
2. Neuroendocrine tumor G2	3-20%	2-20/10 HPF
Poorly differentiated neuroendocrine neoplasms		
1. Neuroendocrine carcinoma G3	>20%	>20/10 HPF
Mixed adenoneuroendocrine carcinomas (MANEC)		

Table 6. The WHO 2017 NET classification

Well-differentiated neuroendocrine tumors	Ki-67 index	Mitotic count
1. Neuroendocrine tumor G1	3%	2/10 HPF
2. Neuroendocrine tumor G2	3-20%	2-20/10 HPF
1. Neuroendocrine tumor G3	>20%	>20/10 HPF
Poorly differentiated neuroendocrine neoplasms		
– Neuroendocrine carcinoma G3	>20%	>20/10 HPF
Mixed neuroendocrine non-neuroendocrine carcinomas (MINEN)		

Table 7. Summary of neuroendocrine-specific markers (Kizilgul et al.)

Common markers	Specific markers
Chromogranin	***Carcinoid tumors***
Chromogranin A	24 hours 5-hydroxyacetic acid in urine
Chromogranin B	24 hours 5-hydroxy-tryptophan in urine
Secretogranin II	Plasma serotonin
Secretogranin III (1B1075)	Insulinoma
Secretogranin IV (HISL-19)	Fast insulin
Secretogranin V (7B2)	Fast pro-insulin
Secretogranin VI (NESP55)	Fast-releasing gastrin
Neuron-specific enolase	Glucagonoma
Pancreatic polypeptides	Fast glucagonoma
Chorionic gonadotropics	VIP-oma

Table 8. Functional neuroendocrine tumors and their products (Kizilgul et al.)

Name	Hormone	Cells	Incidence	Pancreas (%)	Duodenum (%)	Malignancy (%)
Insulinoma	insulin	β	1/1.25	>99		5-11
Gastrinoma	gastrin	G	1/1.5	21-65	6-35	60
Glucagonoma	glucagon	α	<1/5	>99		>70
VIP-oma	VIP	δ	<1/5	85-90	10-15	50
Somatostatinoma	somatostatin	δ	<1/10	50	50	90
Non-functional	neuron-specific enolase, PP	F	1/5	>99		>50

syndromes due to excessive hormonal secretion, also called tumor functionality, was applied to the nomenclature of NETs. Examples include well-differentiated pancreatic tumors that produce insulin, glucagon, and gastrin. Although functionality plays a role in the prognosis of some subsets (e.g., insulinomas are usually very slow-growing), the grade and stage of the tumor determine the biological behavior of functional NETs.

Mixed neuroendocrine non-neuroendocrine neoplasms (MINENs) consist of non-endocrine carcinoma combined with neuroendocrine neoplasm. Usually, both components have a high malignant potential. The condition for the tumor to be classified as MINEN is that each component constitutes at least 30% of the total tumor mass. Adenocarcinomas with scattered neuroendocrine cells are classified as adenocarcinomas with a neuroendocrine component [26,27].

WHO 2022 classification

In 2022, a new WHO classification was introduced and named 2022 WHO Classification of Endocrine and Neuroendocrine Tumors. It is based on a question-and-answer approach. The aim was to provide an easy and precise classification that can be used in real-life pathology. The WHO Classification 2022 approves a 3-tiered grading system for most NETs, in particular those in the gastrointestinal and pancreatobiliary tract, as well as in the upper digestive tract and salivary glands. (Table 9)

Gastroenteropancreatic neuroendocrine tumors have molecular alterations and show prominent site-specific epigenetic changes. The profiles of NECs and NETs are different. Small cell NEC (SCNEC) is characterized by the inactivation of TP53 and/or RB1. Large cell NEC (LCNEC), however, is a more heterogeneous group of tumors and shows a variable genetic profile in different sites of origin. Molecular studies are not necessary for the routine diagnostic process of neuroendocrine neoplasms but may be helpful in specific cases [28].

Table 9. The World Health Organization (WHO) 2022 Epithelial Neuroendocrine Neoplasms Classification for gastrointestinal and pancreatobiliary tract

Neuroendocrine neoplasm	Classification	Diagnostic criteria
Gastrointestinal and pancreatobiliary tract		
Well-differentiated neuroendocrine tumor (NET)	NET, grade 1 NET, grade 2 NET, grade 3	< 2 mitoses/2 mm^2 and/or Ki67 < 3% 2–20 mitoses/2 mm2 and/or Ki67 3–20% > 20 mitoses/2 mm^2 and/or Ki67 > 20%
Poorly differentiated neuroendocrine carcinoma (NEC)	Small cell NEC Large cell NEC	> 20 mitoses/2 mm^2 and/or Ki67 > 20% (often > 70%), and small cell cytomorphology > 20 mitoses/2 mm^2 and/or Ki67 > 20% (often > 70%), and large cell cytomorphology
Upper aerodigestive tract and salivary glands		
Well-differentiated neuroendocrine tumor (NET)	NET, grade 1 NET, grade 2 NET, grade 3	< 2 mitoses/2 mm^2 and no necrosis, and Ki67 < 20% 2–10 mitoses/2 mm^2 and/or necrosis, and Ki67 < 20% > 10 mitoses/2 mm^2 and/or Ki67 > 20%
Poorly differentiated neuroendocrine carcinoma (NEC)	Small cell NEC Large cell NEC	> 10 mitoses/2 mm^2 and/or Ki67 > 20% (often > 70%) and small cell cytomorphology > 10 mitoses/2 mm^2 and/or Ki67 > 20% (often > 55%) and large cell cytomorphology

Conclusions

The different and ever-changing terminology creates difficulties for clinicians and is a prerequisite for the incomparability of the results from further population-based studies. The various definitions recognized the main branches of neuroendocrine neoplasia, the epithelial type that originates in endocrine and non-endocrine organs, and the neural type that originates in neuronal structures. The existence of several classification systems creates confusion among pathologists and clinicians. That is why classification principles have been implemented in the 5th edition of the WHO Classification of Endocrine Tumors.

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