Review article

Changes in the pathomorphological diagnosis of gastrointestinal neuroendocrine neoplasms in 2017

***Anna Nasierowska-Guttmejer*[1, 2]**

[1] *Department of Pathomorphology, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw*
[2] *Department of Pathology, Faculty of Medicine and Health Sciences, Jan Kochanowski University in Kielce*

Correspondence:
Anna Nasierowska-Guttmejer
Department of Pathomorphology, Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw
02-507 Warsaw, ul. Wołoska 137
e-mail: anna.guttmejer@gmail.com

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ABSTRACT

The following changes were introduced in 2017 WHO and TnM classifications:

1. a new group of well-differentiated neuroendocrine tumors with the proliferation index of more than 20% and mitotic count of 20 per 10 hpf (NET G3), formerly classified under neuroendocrine carcinomas (NEC G3)
2. the division of poorly differentiated neuroendocrine tumors (PD NET) with the Ki-67 index of more than 20% into two groups in terms of the degree of differentiation and prognosis: NET G3 and NEC.
3. the replacement of MANEC with MINEN within the mixed group
4. the verification of histological grading (G) criteria
5. new TNM staging criteria, based on ENETS guidelines.

Key words: neuroendocrine tumors, G3 NET, NEC, neuroendocrine carcinoma, Ki-67 proliferation index

INTRODUCTION

Gastro-entero-pancreatic neuroendocrine neoplasms/neuroendocrine neoplasms (GEP NEN/NEN), or gastro-entero-pancreatic tumors/neuroendocrine tumors (GEP NET/NET), are derived from 15 types of diffuse endocrine system cells (DEC) dispersed across the digestive tract and the pancreas. Divided into hormonally active and inactive tumors, each with its own organ-specific clinical course and prognosis, they share a common histopathological classification of the World Health Organization (WHO), which is based on two microscopic traits:

- morphological image
- proliferative activity.

The classification distinguishes between well-differentiated and poorly differentiated GEP NENs:

- well-differentiated low-grade tumors (G1)
- moderately differentiated intermediate-grade tumors (G2)
- poorly differentiated high-grade tumors (G3).

The above classification forms the basis of treatment guidelines published by the European Neuroendocrine Tumor Society (ENETS) [1–3], American bodies such as the North American Neuroendocrine Tumor Society (NANETS) and the National Comprehensive Cancer Network (NCCN) [4], as well as the Polish Network for Neuroendocrine Tumors [5, 6]. The treatment of neuroendocrine neoplasms is decided by an interdisciplinary team of diagnosticians, including radiologists and pathomorphologists, as well as clinicians, endocrinologists, gastroenterologists, surgeons, and clinical oncologists.

Neuroendocrine neoplasms are all potentially malignant, but form a heterogeneous group in terms of clinical presentation, prognosis, and treatment. Removed by polypectomy, well-differentiated neuroendocrine tumors of the stomach (NET G1, 1 NEN type) are not associated with a risk of metastasis and have a 5-year survival rate of 100% [7]. Likewise, when treated with the method of endoscopic submucosal dissection, well-differentiated NENs of the rectum show a high 5-year survival rate of 75–100%. The actual prognosis crucially depends on tumor size, the depth of invasion into the rectal wall, and the presence of lymph node metastases [8]. For polyps with diameters greater than 21 mm, the risk of metastasis is between 60 and 80%. Well-differentiated hormonally inactive pancreatic neuroendocrine tumors (PanNETs) grow at a slow pace, resulting in the 5-year survival rate of more than 95% [9]. Well-differentiated neuroendocrine tumors of the small intestine, on the other hand, are a case apart among the NENs. In the absence of liver metastases, they usually manifest as small, multifocal, asymptomatic lesions. When liver metastases are present, however, symptoms of the carcinoid syndrome are diagnosed in 20 to 30% of cases. The 5-year survival rate for small-intestine NET patients equals 59–74%, while the 10-year survival rate is 15–25% and 60% for cases with and without metastasis, respectively [10]. Unlike well-differentiated tumors, neuroendocrine carcinomas have a bad prognosis and a 5-year survival rate below 50%. In rare pancreatic neuroendocrine carcinomas (PanNEC), the 5-year survival rate is c. 33%, the 10-year survival rate – 17%, and the 20-year survival rate – as low as 10%. Surgical removal of the primary tumor helps prolong the life of the patient, with the median of 1.2 year vs. 8.4 years, and 1 vs. 4.8 years in the presence of metastases. No differences in terms of survival time are observed between patients who undergo PanNEC-related enucleation and those treated with surgical removal (median: 10.2 vs. 9.2, respectively) [11]. In the colon, the most frequently diagnosed types include advanced neuroendocrine carcinomas with a 5-year survival rate of 40–70%; the mean survival time equals 261 months for locally advanced carcinomas, 36 months if lymph nodes are invaded, and 5 months in the presence of remote metastases [8]. The actual clinical course depends on the location and stage (pTnM) at the moment of diagnosis. Neuroendocrine neoplasms require oncological treatment, chemotherapy or (thanks to the increasingly better known role of the mTor pathways) the use of molecularly targeted drugs or a combined treatment with chemotherapy [12]. Accordingly, all NEN cases call for individual evaluation and clinical decision.

2000 AND 2010 NEN CLASSIFICATIONS

From 2000 onward, gastrointestinal neuroendocrine neoplasms were diagnosed based on their degree of differentiation and grading, as assessed by the Ki-67 proliferation index [13]. Tumors previously lumped together as "carcinoids" were thus divided into well-differentiated endocrine tumors/carcinomas (WDET/WDEC) and poorly differentiated endocrine carcinomas/small-cell carcinomas (PDEC) [14]. Adopted in 2010, a new WHO classification of gastrointestinal tumors introduced a twofold division of NENs into well-differentiated neuroendocrine tumors (WD-NET) and poorly differentiated neuroendocrine tumors (PD NET) [15, 16]. The architecture and cytological features of WDNETs resemble normal neuroendocrine cells that make up organoid structures. Their morphological image shows trabecular, rosette, pseudoglandular, and solid histological patterns and cell nuclei contain granular chromatin with a characteristic salt-and-pepper pattern. PD NETs, on the other hand, are defined as neuroendocrine carcinomas (NEC), which resemble lung carcinomas and are

divided into small-cell and large-cell subtypes. The 2010 WHO classification also distinguished a separate group of mixed adenoneuroendocrine carcinomas (MANEC).

Another microscopic feature used to classify NENs is histological grading (G). In 2010, in accordance with the ENETS/WHO guidelines, the following assessment criteria were adopted for this parameter:

- the Ki-67 proliferation index, based on an immunohistochemical assay
- the mitotic count [17].

With these two features in mind, the 2010 WHO classification divided well-differentiated neuroendocrine tumors into WDNET G1 and WDNET G2 subtypes. The G3 grade was assigned to neuroendocrine carcinomas (NEC). It is worth noting that the degree of differentiation and grading are parameters that apply only to NENs and differ from those valid for non-neuroendocrine tumors, such as exocrine gastrointestinal adenocarcinomas.

A third microscopic trait useful in clinical practice is the stage of the cancer (TNM), as assessed on the basis of postoperative material following the classification criteria proposed by ENETS and the AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) [18–20]. For WDNETs, these are organ-specific and defined by separate classifications drawn up for neuroendocrine tumors; for PD NET/NECs and MANECs, they are assessed based on criteria common with exocrine organ carcinomas.

The above three microscopic parameters: the degree of differentiation, histological grading (G), and TNM stage, are prognostic and predictive factors that set the group of neuroendocrine neoplasms apart from non-neuroendocrine carcinomas.

2017 NEN CLASSIFICATION

Observations of NEN patients and their response to treatment led to important changes in the 2017 WHO classification [21] and the 8th edition of the TNM staging system recommended by the AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) [22–27]. The modification of previously discussed systems allowed to better divide patients into distinct groups in terms of effective treatment methods. The following changes were introduced:

1. A new group of well-differentiated neuroendocrine tumors with the proliferation index of more than 20% and mitotic count of 20 per 10 hpf (NET G3).
2. The division of poorly differentiated neuroendocrine tumors (PD NET) with the Ki-67 index of more than 20% into two groups in terms of the degree of differentiation and prognosis: NET G3 and NEC.

TABLE 1.
WHO classification of gastrointestinal neuroendocrine tumors before 2017 [15, 16].

WHO 1980	WHO 2000	WHO 2010
1. Carcinoid 2. For pancreatic tumors: • islet cell tumor • adenoma/carcinoma	1. Well-differentiated endocrine tumor (WDET) 2. Well-differentiated endocrine carcinoma (WDEC) 3. Poorly differentiated endocrine carcinoma (PDEC)	1. Well-differentiated neuroendocrine tumor G1 (NET G1) 2. Well-differentiated neuroendocrine tumor G2 (NET G2) 3. Neuroendocrine carcinoma (NEC G3) Poorly differentiated NEN (large cell or small cell type)
3. Mucocarcinoid 4. Mixed forms carcinoid-adenocarcinoma	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
5. Pseudotumor lesions	5. Tumor-like lesions	5. Hyperplastic and preneoplastic lesions

TABLE 2.
Histological grading of gastrointestinal neuroendocrine neoplasms based on pre-2017 criteria [15, 16].

Histological grading of nETs	Mitotic activity/mitotic count/10 hpf	Ki-67 index/% of cells
G1 – well-differentiated, low grade	< 2	≤ 2
G2 – moderately differentiated, intermediate grade	2–20	3–20
G3 – poorly differentiated, high grade	> 20	> 20

3. The replacement of MANEC with MINEN within the mixed group.
4. The verification of histological grading (G) criteria.
5. New TNM staging criteria 2017.
6. The elimination of the group of tumor-like, hyperplastic, and preneoplastic lesions.

HISTOLOGICAL TYPES ACCORDING TO THE 2017 WHO CLASSIFICATION

Grading played a crucial role in classifying NENs into prognostic groups under the WHO 2010 classification system. In accordance with these guidelines, all tumors with the proliferation index of more than 20%, regardless of their morphological presentation, were labelled as "neuroendocrine carcinomas" (NEC). In recent years, however, the NEC group has been shown to be heterogeneous [28–33]. Some NECs are well-differentiated and have a Ki-67 index higher than 20%; such patients have a better prognosis than those who are diagnosed with poorly differentiated small- or large-cell neuroendocrine carcinomas with the proliferation index below 20%. Accordingly, the 2017 WHO classification introduced a new category, NET G3, to encompass tumors that show no or fewer molecular alterations in the *TP53* and *RB1* genes as compared with other NECs [34]. These neoplasms are characterized by the mitotic count of 20 or above per 10 hpf and the Ki-67 index of more than 20 but often less than 55%. In contrast, neuroendocrine carcinomas (NEC G3) have a poorly differentiated morphology of the small- or large-cell carcinoma type and the Ki-67 index of more than 55%. Konukiewitz et al. [34] have demonstrated the presence of type 2a somatostatin receptors in well-differentiated tumors and in 16% of poorly differentiated tumors. Molecular alterations in the *TP53* and *RB1* genes, the immunohistochemical expression of *TP53* and the loss of *RB1*, were observed in PD NENs. Genes in WDNENs were normal. Table 3 shows the 2017 WHO classification of the NENs of the digestive system. The 2017 WHO classification distinguishes three NEN types:

1. Well-differentiated tumors of the NET G1, NET G2, and NET G3 type.
2. Poorly differentiated NEC G3 tumors further subdivided into large- and small-cell types.
3. Mixed neuroendocrine-non-neuroendocrine neoplasms (MINEN).

Well-differentiated NENs can be characterized by a high, intermediate, or low histological grade: NET G3, NET G2, and NET G1. They form organoid morphological structures and present markers of neuroendocrine differentiation, such as a diffuse and intense reaction to synaptophysin and, more often than not, to chromogranin A. They may also produce hormones that form the basis for the diagnosis of hormonally active tumors and their accompanying clinical syndromes. In terms of clinical presentation, PanNETs, in particular, are divided into the following tumor types:

- insulinoma
- glucagonoma
- gastrinoma
- VIP-oma
- serotonin-producing tumors with or without the presence of the carcinoid syndrome.

The NET G1 and NET G2 types are characterized by the Ki-67 index of up to 20% and the mitotic count of max. 20 per 10 hpf; the corresponding figures for the NET G3 type are more than 20% and 20 per 10 hpf, respectively. Detailed classification criteria are shown in table 3. In a study published in 2017, Milan scholars established a correlation between overall survival (OS) and the Ki-67 index over 20%, depending on the degree of differentia-

TABLE 3.
2017 WHO classification of the neuroendocrine neoplasms of the digestive tract NEN [21].

Histological type/grade (G)	Ki-67 index	Mitotic index
Well-differentiated neuroendocrine neoplasms (NEN)		
NET G1 NET G2 NET G3	< 3% 3–20% > 20%	< 2 2–20 > 20
Poorly differentiated neuroendocrine neoplasms/neuroendocrine carcinomas (NEC)		
NEC G3 small-cell type large-cell type	> 20%	> 20
Mixed neuroendocrine-non-neuroendocrine neoplasms (MINEN)		

tion and the Ki-67 value. OS for NET G3 was shown to equal 43.6 months; the corresponding values for NECs with a Ki-67 index of between 20 and 55% and 55% and higher were 24.5 and 5.3 months, respectively.

Poorly differentiated neuroendocrine neoplasms, referred to as neuroendocrine carcinomas (NEC G3), normally present a large atypia in small-cell carcinomas and medium to low atypia in large-cell types, along with a strong or weak synaptophysin expression and weak or no reaction to chromogranin A. They rarely produce hormones and the expression of exocrine enzymes is usually low. The grading indicators for NEC G3 are as follows:

- Ki-67 index: more than 20%
- mitotic count: more than 20 per 10 hpf.

Mixed tumors of the MINEN type, neuroendocrine and non-neuroendocrine carcinomas, include both elements in at least 30% of the volume. They are usually high-grade (G3), but may also encompass G1 or G2 components. In the case of pancreatic cancer, the diagnosis usually includes mixed ductal-neuroendocrine carcinoma or mixed acinar-neuroendocrine carcinoma components.

Histological grading (G)

The histological grading of NENs is assessed based on the 2017 WHO classification criteria, with an emphasis on 2 features that need to be listed in the pathomorphological report. These include the mitotic count per 10 hpf and the ki-67 index. Detailed assessment criteria are shown in table 4.

TABLE 4.
Histological grade assessment criteria in accordance with the 2017 WHO classification.

Histological grade assessment criteria in accordance with the 2017 WHO classification.	
Mitotic count per 10 hpf measured: • at 40 x magnification, i.e. an area of 2 mm^2 • it is essential to select 10 fields with the greatest mitotic activity (i.e. hot spots) from among 50 hpf	The ki-67 index the percentage of cells showing the immunohistochemical expression of the anti-ki-67 antibody (MiB1) in hot spots, measured in 500–2000 tumor cells

In grading assessment, attention should be paid not only to classification criteria but also to the measurement method [35]. Semi-quantitative, subjective, naked-eye assessments are not recommended in the estimation of the Ki-67 index in NENs. The accepted method involves counting tumor cells that show the immunohistochemical expression of the MIB1 antibody (anti-Ki-67) within the field of at least 500 tumor cells and determining the percentage of positive cells among them. This "manual counting method" is objective and comparable with computer techniques performed on scanned samples. Other techniques include the preparation of a tumor sample and the simultaneous performance of 2 immunohistochemical assays, testing the cytoplasmic color reaction to synaptophysin, and measuring the nuclear reaction to the presence of MIB1. If the grades determined by the Ki-67 index and the mitotic count differ, the former is usually preferred.

TNM stage

The TNM staging of well-differentiated neuroendocrine neoplasms follows ENETS criteria and the 8th edition of the AJCC/UICC 2017 TNM classification [21]. Qualification criteria in both 2010 systems differed. The current AJCC/UICC 2017 TNM classification is based on guidelines similar to those defined by the ENETS. The T trait assessment is based on tumor size and extent (depth of invasion). Table 5 shows the criteria based on 2017 guidelines. Neuroendocrine carcinomas and mixed tumors MINEN are graded according to the TNM staging system for non-neuroendocrine neoplasms.

TABLE 5.
AJCC/UICC 2017 TNM classification for pancreatic neuroendocrine tumors [21, 36].

T trait in the AJCC/UICC 2017 TNM grading system (according to the TNM system defined by ENETS)
TX – tumor cannot be assessed. T1 – carcinoma in situ, diameter < 2 cm. T2 – carcinoma in situ, diameter more than 2 but less than 4 cm. T3 – carcinoma in situ and/or the peripancreatic fat tissue, diameter of 4cm and above, or invading the duodenum/the bile duct. T4 – carcinoma spreads beyond the serous surface of the peritoneum (serosa) or to adjacent organs or large vessels. **Comments**: adjacent organs (stomach, spleen, colon, adrenal glands), walls of large vessels (celiac trunk, superior mesenteric artery).

CONCLUSIONS

Gastrointestinal neuroendocrine neoplasms are diagnosed on the basis of two current systems: the histopathological WHO 2017 classification and the 8th edition of the AJCC/UICC 2017 TNM staging system laid down by the ENETS.

New criteria distinguish a separate group of NET G3 tumors, previously classed under neuroendocrine carcinomas (NEC) – a group of well-differentiated neoplasms with the Ki-67 index of over 20% and mitotic count of more than 20 per 10 high-power fields. This division allows for an improved division of patients into prognostic and predictive groups in terms of optimal treatment methods.

Prognostic factors that determine NEN progression include:

1. Histological type defined by the degree of tumor differentiation and its grading (G), based on the Ki-67 index and the mitotic count per 10 high-power fields.
2. TNM stage assessed on the basis of postoperative material, depending on tumor size and location and the presence of metastases in lymph nodes and/or other remote locations.

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A histological report from the examination of NEN postoperative material should include the following data (according to the 2017 guidelines of the Polish Network for Neuroendocrine Tumors) [5]:

- clinical data: anatomical location, clinical symptoms in the case of hormonally active neoplasms, and the name of the endoscopic of surgical procedure
- macroscopic traits: description of the tumor with its location, cross-section, relationship to neighboring tissue, and surgical margins in accordance with organ-specific guidelines
- microscopic traits: histological type with a description of the histoformative structures of the tumor and cell type, assessment of the Ki-67/MiB1 index and mitotic count in high-activity areas (hot spots) in accordance with the ENETS/WHO system (G1–G3) and the assessment of the degree of histological differentiation
- description of the histopathological invasiveness parameters: angiolymphoid invasion, neural invasion, necrosis, invasion of the follicle (pseudofollicle), and the depth of invasion in the organ and adjacent tissues/organs
- immunohistochemical expression: obligatory for chromogranin A, synaptophysin and Ki-67 with the use of the MIB1 antibody and optional for other hormonal markers
- description of metastases, if present
- description of surgical margins
- additional parameters, such as inflammations and other neoplastic components, if present.

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