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Relation between WHO Classification and Location- and Functionality-Based Classifications of Neuroendocrine Neoplasms of the Digestive Tract

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Keywords
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Abstract
Practice of neuroendocrine neoplasms (NENs) of the digestive tract, which comprise of a highly diverse group of tumors with a rising incidence, faces multiple biological, diagnostic, and therapeutic issues. Part of these issues is due to misuse and misinterpretation of the classification and terminology of NENs of the digestive tract, which make it increasingly challenging to evaluate and compare the literature. For instance, grade 3 neuroendocrine tumors (NETs) are frequently referred to as neuroendocrine carcinomas (NECs) and vice versa, while NECs are, by definition, high grade and therefore constitute a separate entity from NETs. Moreover, the term NET is regularly misused to describe NENs in general, and NETs are frequently referred to as benign, while they should always be considered malignancies as they do have metastatic potential. To prevent misconceptions in future NEN-related research, we reviewed the most recent terminology used to classify NENs of the digestive tract and created an overview that combines the classification of these NENs according to the World Health Organization (WHO) with location- and functionality-based classifications. This overview may help clinicians and researchers in understanding the current literature and could serve as a guide in the clinic as well as for writing future studies on NENs of the digestive tract. In this way, we aim for the universal use of terminology, thereby providing an efficient foundation for future NEN-related research.

Introduction

Neuroendocrine neoplasms (NENs) are tumors that originate from neuroendocrine cells or show neuroendocrine differentiation and have an annual incidence of 2–7 cases per 100,000 persons, which keeps rising because of increased incidental discovery and improved pathological classification [1–5]. They are found throughout

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the body, with the majority (~67%) of NENs arising in the digestive tract, including the gastrointestinal tract, hepatobiliary tract, and pancreas, in which, at least fifteen different types of neuroendocrine cells have been described [1, 2, 6, 7]. Due to the diverse biological activities of these cell types, NENs of the digestive tract, which are epithelial in origin, represent a heterogenous group of neoplasms and induce a wide variety of disease manifestations [6]. Consequently, numerous efforts have been made to allow easy classification of NENs of the digestive tract and to categorize them according to their location and functionality. In addition, molecular subtyping of NENs has contributed to our understanding of these neoplasms and in particular to the understanding that neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) constitute different entities of NENs. However, as the classification systems have been changed rigorously multiple times over time and because the number of related studies mirrors the incidence trend and therefore rapidly advances, several different as well as overlapping terms have been introduced concurrently. As a result, the terminology for the classification of NENs of the digestive tract is regularly misused or misconceived, making it increasingly challenging to evaluate and compare the literature. For this reason, this review evaluates the most recent terminology used for the classification of NENs of the digestive tract, including the novel WHO classification of NENs of 2022, and aims to provide an overview of the terminology that could be used as a guidance by clinicians and researchers for future studies.

Classification according to the WHO

The most widely applied classification system of NENs of the digestive tract is established by the World Health Organization (WHO), a recognized institute for the development of standardized terminology. The first WHO classification for NENs of the digestive tract appeared in 1980 and has henceforth been frequently updated, with the most recent versions originating from 2010, 2017, 2019, and 2022 [8–10].

WHO Classification of 2010

In the WHO classification of 2010, which the WHO developed in collaboration with the European Neuroendocrine Tumour Society, NENs of the digestive tract were categorized according to the proliferation status of the tumor cells [8]. Assuming that the proliferation status, or grade, mainly reflects the biological aggressiveness of the tumor, the proliferation index was the main feature to distinguish between high-grade and low-grade NENs. The proliferation index was evaluated using the mitotic and Ki-67 indices, which both represent the percentage of dividing cells [8]. The mitotic index comprises the number of mitoses per 10 high-power microscopic fields, while the Ki-67 index involves the percentage of cells staining positive for the proliferation marker Ki-67, as usually evaluated in a field of 500–1,000 tumor cells [11]. In case the Ki67 index and mitotic index showed discrepant results, the index with the highest grade was used for grading. A more detailed description of how to determine and interpret mitotic and Ki-67 indices is referred to in previous reports [12, 13]. NENs with relatively low (Table 1) mitotic and/or Ki-67 indices were considered to be low (grade 1) or intermediate grade (grade 2), while NENs with high mitotic and/or Ki-67 indices were considered high grade (grade 3). Grade 1–2 NENs of the digestive tract were generally believed to be well differentiated and were called NETs, while grade 3 NENs were typically considered poorly differentiated and were called NECs. NECs were subdivided into large cell-neuroendocrine carcinomas (LC-NECs) and small cell-neuroendocrine carcinomas (SC-NECs). In addition, the WHO classification of 2010 included a category of mixed adenoneuroendocrine carcinomas (MANECs), which like NECs, were poorly differentiated and were characterized by the presence of both adenocarcinoma and neuroendocrine neoplastic cells, with each histological subtype accounting for at least 30% of the tumor [8, 11].

WHO Classifications of 2017 and 2019

Despite being practically usable and effective in predicting patient survival, the WHO classification of 2010 led to confusion about the discrepancy between "grade" and "differentiation" [11]. While the grade of an NEN reflects the biological aggressiveness of the neoplasm in terms of their potential for growth and spread, the differentiation status of a NEN refers to the morphologic resemblance of the neoplastic cells to their cells of origin [11]. For NENs of the digestive tract, well-differentiated cells show minimal-to-moderate atypia, express general neuroendocrine differentiation markers, and could (but not necessarily) produce hormones. Poorly differentiated cells, on the other hand, are highly atypical and show a different pattern of expression of general neuroendocrine differentiation markers as compared to well-differentiated cells (e.g., faint instead of diffuse expression) [11]. The expression of general neuroendocrine differentiation markers is assessed by immunohistochemistry and mainly involves stains for INSM1, synaptophysin, and

Table 1. WHO classification of NENs of the digestive tract[a]

WHO classification of 2010 [8]				WHO classifications of 2017 [14], 2019 [15], and 2022 [16]			
	grade	Ki67 index[b,c], %	mitotic index[b,d]		grade	Ki67 index[b,c], %	mitotic index[b,d]
Well-differentiated NEN				Well-differentiated NEN			
NET	1	<3	<2	NET	1	<3	<2
	2	3–20	2–20		2	3–20	2–20
					3	>20	>20
Poorly differentiated NEN				Poorly differentiated NEN			
NEC	3	>20	>20	NEC	High[e]	>20	>20
SC				SC			
LC				LC			
MANEC				MiNEN	1–3	<3–>20	<2–>20

MANEC, mixed adenoneuroendocrine carcinoma; LC, large cell; MiNEN, mixed endocrine non-endocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SC, small cell; WHO, World Health Organization. [a]This table is adapted from the study by Choe et al. [11]. [b]In case the Ki67 index and mitotic index show discrepant results, the index with the highest grade should be used for classification. [c]Per 500–1,000 tumor cells. [d]Per ten high-power fields. [e]Though in practice, NECs were already widely regarded as high grade following the introduction of the WHO classifications of 2017 and 2019, the latter classifications in theory still allowed NECs to be categorized into grades 1–3.

chromogranin, which are expressed by most NENs [16]. The majority of NENs express chromogranin A, yet some produce chromogranin B and/or C instead. In addition, all epithelial NENs produce keratins, which may be identified by AE1/AE3, CAM5, CK7, or CK20 stains [16]. These stains, however, could be faint, and (double-)negative staining of CK7 and/or CK20 is frequently observed [17, 18], implicating that negative stains do not rule out an epithelial NEN and that stains for large spectrum cytokeratin (e.g., BerEP4) may be preferred.

Importantly, the WHO classification of 2010 did not consider a subset of NENs that were morphologically well-differentiated but showed a high mitotic (>20) or Ki-67 (>20%) index level [9, 11]. Technically, the WHO classification of 2010 would have described these NENs as grade 3, whereas based on morphology and follow-up, they should have been classified as NETs. Interestingly, this particular group of NET-like neoplasms with high proliferation rates comprised a distinct entity based on clinical and molecular features, for example, responding differently to platinum-based chemotherapy than poorly differentiated NECs, and seemed to occur more frequently in the pancreas compared to other sites of the digestive tract [11, 19, 20]. This resulted in the release of a new WHO classification for endocrine organs in 2017, which was specifically devised for pancreatic NENs, as well as in an updated WHO classification of tumors of the digestive tract in 2019, which not only applied for pancreatic NENs but for all NENs of the digestive tract [14, 15]. In these classification systems, two important revisions were made (Table 1). First, the new system recognized the entity "NET grade 3," a NEN with well-differentiated morphology and immunophenotype, and a high proliferation rate. As such, well-differentiated NENs with a higher mitotic or Ki-67 index level were no longer automatically classified as NECs. Secondly, MANECs were renamed mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs, MeNENs), thereby acknowledging the facts that they could have a non-endocrine component other than adenocarcinoma (e.g., squamous) as well and that the neuroendocrine component may be (partially) well differentiated [14, 20].

WHO Classification of 2022

Following recent advances in NEN-related research, especially in the field of molecular and biochemical testing, the WHO recently released the WHO classification of NENs in 2022 [16]. The WHO classification of NENs of 2022 includes a complete chapter on NENs of non-endocrine organs (e.g., the gastrointestinal tract) and generally mimics the classification of NENs into NETs, NECs, and MiNENs as included in the WHO classifications of 2017 and 2019 (Table 1) [16]. One minor revision involves the fact that NECs are, by definition, high grade in the WHO classification of 2022. Though in

practice, NECs were already widely regarded as high grade following the introduction of the WHO classifications of 2017 and 2019, the latter classifications in theory still allowed NECs to be categorized into grades 1–3 [14, 16]. The latter was proven redundant as poorly differentiated NENs should be referred to as NECs disregarding their Ki67/mitotic index classification. In this way, the WHO further highlights the distinction between NETs and NECs, thereby aiming to prevent future misconceptions of the separate entities.

Likewise, the WHO classification of 2022 aims to provide pathologists tools to distinguish grade 3 NETs and NECs, which may be challenging, as grade 3 NETs could resemble LC-NECs, and the proliferative index alone cannot distinguish both NENs [16]. The presence of a prior or coexisting grade 1–2 NET component in the tumor would favor the diagnosis of NET grade 3, whereas a coexisting conventional carcinoma component would favor the diagnosis of NEC. The expression of somatostatin receptors and/or the loss of expression of ATRX, DAXX, or menin, as assessed by immunohistochemical stains, can be useful to distinguish a NET from an NEC [16]. Moreover, testing for the presence of unique DNA alterations in tumors by next-generation or whole-genome sequencing, as well as assessing additional clinical information, including imaging data, may help in distinguishing NETs from NECs [16].

Noteworthily, after the release of the WHO classification of 2017, 2019, and 2022, studies still frequently used outdated versions of the WHO classification. Most importantly, grade 3 NETs of the digestive tract were still commonly considered as NECs, resulting from the fact that grade 3 was exclusively assigned to NECs in the WHO classification of 2010. Moreover, the term NETs was still regularly misused to describe NENs in general. When reviewing studies reporting on NETs, it is therefore highly advised to assess whether NECs or MiNENs were included as well and whether the authors should have used the term NENs instead of NETs. Also, the term carcinoid, which originates from the WHO classification of 1980, remains present in many original papers and reviews on NENs of the digestive tract. However, recent WHO classifications of NENs of the digestive tract, including those of 2010, 2017, 2019, and 2022, abandoned this term as it caused confusion by being differentially used by pathologists and clinicians. Pathologists assigned this term to tumors with neuroendocrine features, whereas clinicians used it to describe serotonin-producing tumors that caused carcinoid syndrome [21, 22]. Consequently, the use of the term carcinoid is obsolete in the context of NENs of the digestive tract. Of note, for NENs of the lung, the term carcinoid has been updated and is still in use [23]. Another frequently occurring misconception is that NETs are referred to as being benign, as they are generally slow-growing tumors and have a more favorable prognosis even when detected in a late stage. However, since they do have the capability to metastasize, and many patients eventually die of the disease, they should always be considered malignancies.

Classification Based on Location

In addition to the WHO classifications, NENs of the digestive tract are frequently categorized and named according to their location (shown in Fig. 1). Usually, the abbreviation used to describe the location of NENs (which officially are not acknowledged by WHO) is placed in front of the WHO terminology (Table 2). To illustrate, NENs located in the stomach, small intestines, colorectum, appendix, and pancreas are generally called gastroenteropancreatic-NENs (GEP-NENs), which could involve gastroenteropancreatic-NETs (GEP-NETs), gastroenteropancreatic-NECs (GEP-NECs), and gastroenteropancreatic-MiNENs (GEP-MiNENs). In the same way, though less frequently used, NENs of the stomach, small intestines, colorectum, and appendix may be referred to as gastrointestinal-NENs (GI-NENs), consisting of gastrointestinal-NETs (GI-NETs), gastrointestinal-NECs (GI-NECs), and gastrointestinal-MiNENs (GI-MiNENs). The terms "GEP-NEN" and "GI-NEN" highly overlap and though they usually appear to differ in the in-/exclusion of pancreatic NENs, both terms are frequently used interchangeably or by preference and a clear distinction between both terms is lacking. The TNM staging criteria, which are specific for GEP-/GI-NETs, vary per site and are of high importance for clinical management. A comprehensive overview of site-specific staging criteria of GI-NETs [24] and pancreatic-NETs [25] can be found on Cancer.Net. NENs located in other sites of the digestive tract, such as the extrahepatic bile ducts, gallbladder, and liver are generally referred to as hepatobiliary-NENs rather than GEP-/GI-NENs.

Esophagus

Esophageal-NENs (E-NENs, eNENs) are relatively rare, predominantly develop sporadically, and have an estimated annual incidence of 0.09–0.3 cases per 100,000 persons (Table 3). They mainly comprise esophageal-NECs (E-NECs) and esophageal-MiNENs (E-MiNENs), with the latter showing a similar mutational landscape as small cell lung cancer [16, 26–31]. E-MiNENs either

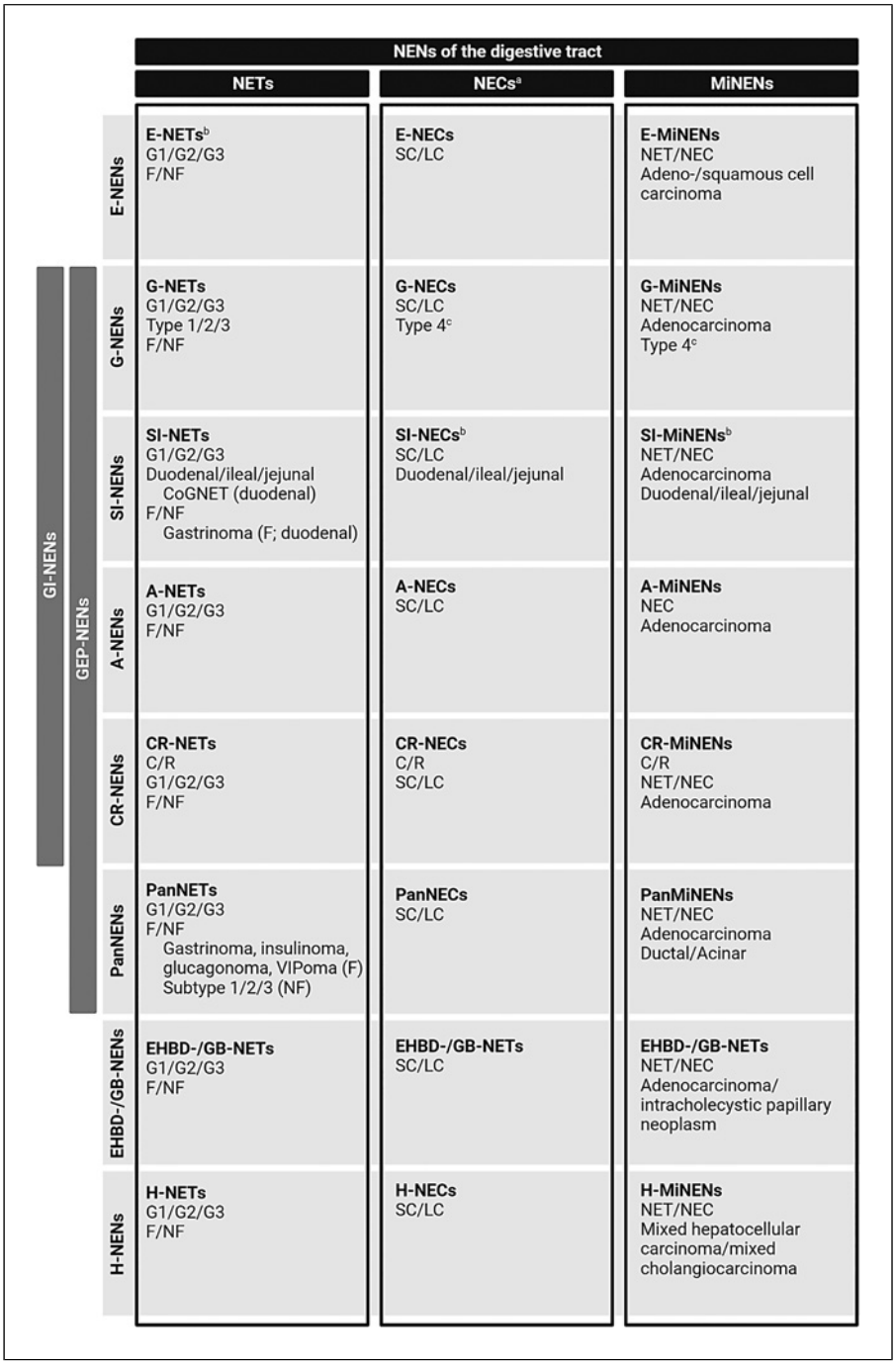

Fig. 1. Overview of the classification of NENs of the digestive tract. Classification is based on the WHO classification of 2022, location-, and functionality-based classifications of NENs of the digestive tract. [a]By definition, high grade. [b]Extremely rare/questionable existence. [c]G-NECs and G-MiNENs are occasionally referred to as type 4 G-NETs, though the use of this term is outdated as G-NECs and G-MiNENs are poorly differentiated and by definition, not a NET. Created with BioRender.com. A, appendiceal; CR, colorectal; C, colonic; CoGNET, composite gangliocytoma/neuroma and neuroendocrine tumor; E, esophageal; EHBD, extrahepatic bile duct; F, functional; G, gastric; GB, gallbladder; GEP, gastroenteropancreatic; GI, gastrointestinal; H, hepatic; LC, large cell; MiNEN, mixed neuroendocrine non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NF, nonfunctional; Pan, pancreatic; R, rectal; SC, small cell; SI, small intestine; VIP, vasoactive intestinal peptide.

Table 2. Abbreviations used to classify NENs of the digestive tract according to the their functionality, location, and WHO classification of 2022

Functionality	Location	WHO (2022) [16]
Functional (F) Nonfunctional (NF)	Esophageal (E) Gastric (G) Small intestine (SI) Extrahepatic bile duct (EHBD) Gallbladder (GB) Hepatic (H) Appendiceal (A) Colorectal (CR) Colonic (C) Rectal (R) Pancreatic (Pan)[a] Gastroenteropancreatic (GEP)[b] Gastrointestinal (GI)[c]	Neuroendocrine neoplasm (NEN) Neuroendocrine tumor (NET) Neuroendocrine carcinoma (NEC) Small cell (SC) Large cell (LC) Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN)

WHO, World Health Organization. [a]Pancreatic-NETs should preferentially be abbreviated as PanNETs instead of P-NETs, as the latter abbreviation resembles the abbreviation used to refer to the distinct primitive neuroectodermal tumors (PNETs). [b]Generally includes G-, SI-, A-, CR-, and P-NENs. [c]Generally includes G-, SI-, A-, and CR-NENs.

Table 3. Incidence, immunohistochemical profile, and genetic associations of NENs of the digestive tract

Location	Annual incidence (cases per 100,000 persons)	Immunohistochemical profile	Constitutional genetic associations
E-NENs	0.09–0.3	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20	
G-NENs	0.31–0.43	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20, VMAT2 (NET)	MEN1 (Type 2 G-NETs)
SI-NENs	1.17–1.72	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20, ISL1 (duodenum), PDX1 (duodenum), ARX (duodenum), CDX2 (NET), 5-HT (NET), somatostatin (NET), gastrin (NET)	MEN1 NF1 (somatostatinomas) *MUTYH*[a]
A-NENs	0.95–1.37	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20	
CR-NENs	0.41–0.46 (colon) 0.32–0.51 (rectum, Western countries) 1.82 (rectum, Asian countries)	Syn, CgA/B, INSM1, AE1/AE3, CAM5.2, CK7, CK20, PSAP, CDX2, SATB2, glucagon (NET), PP (NET)	Lynch syndrome Familial adenomatous polyposis
PanNENs	0.8–0.94	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20, ISL1, PDX1, CDX2, ARX (NET), glucagon (NET), insulin (NET), somatostatin (NET), PP (NET), VIP (NET), gastrin (NET)	MEN1 NF1 Tuberous sclerosis Von Hippel-Lindau disease
EHBD-/GB-NENs	0.06	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20	
H-NENs	<0.01	Syn, CgA, INSM1, AE1/AE3, CAM5.2, CK7, CK20	

A-NEN, appendiceal neuroendocrine neoplasm; CgA, chromogranin A; CR-NEN, colorectal neuroendocrine neoplasm; E-NEN, esophageal neuroendocrine neoplasm; EHBD-NEN, extrahepatic bile duct neuroendocrine neoplasm; G-NEN, gastric neuroendocrine neoplasm; GB-NEN, gallbladder neuroendocrine neoplasm; H-NEN, hepatic neuroendocrine neoplasm; MEN1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1; PanNEN, pancreatic neuroendocrine neoplasm; SI-NEN, small-intestine neuroendocrine neoplasm; Syn, synaptophysin. [a]Contrasting evidence.

involve mixed adenocarcinoma-NECs, mixed squamous-cell carcinoma-NECs, or mixed adenocarcinoma-NETs [16]. Of note, only little evidence supports the presence of esophageal-NETs (E-NETs). For example, Wu et al. [32] recently claimed to identify one E-NET in a cohort of 39 E-NENs, though this E-NET was found by biopsy only, with no residual tumor being detected during additional endoscopic examination. As further evidence is lacking, this raises the question whether E-NETs are in fact an existing entity.

Stomach

Gastric-NENs (G-NENs, gNENs), having an incidence of 0.31–0.43 cases per 100,000 persons per year, mainly originate from enterochromaffin-like (ECL) cells [30, 31]. In line with the WHO classification of 2022, G-NENs comprise gastric-NETs (G-NETs), gastric-NECs (G-NECs), and gastric-MiNENs (G-MiNENs). Of these, G-NETs are frequently classified according to an additional distinct classification system, which divides G-NETs into three different subtypes, based on the pathogenesis of the neoplasms. Type 1 G-NETs account for 70–80% of all G-NETs, rarely metastasize and develop in the context of chronic atrophic corpus gastritis, during which hypergastrinemia flourishes [7, 33]. Type 1 G-NETs are often multifocal, and adjacent non-tumoral gastric mucosa shows hyperplasia of neuroendocrine cells. Type 2 G-NETs are less common (5–8% of all G-NETs) and are similar to type 1 G-NETs with regards to cellular composition and the association with hypergastrinemia, though they more frequently metastasize and are associated with multiple endocrine neoplasia type 1 (MEN1) and Zollinger-Ellison syndrome [34–36]. Type 3 G-NETs are not associated with hypergastrinemia or MEN1. They account for 14–25% of all G-NETs and, importantly, have the greatest tendency to metastasize. All three types of G-NETs may grow from either the gastric fundus or the gastric corpus, with the gastric fundus being a predilection side for type 1 and type 2 G-NETs [37]. As hyperplasia of the surrounding mucosa is commonly observed in type 1 and type 2 G-NETs but not in type 3 G-NETs, a biopsy/analysis of surrounding fundic and gastric mucosa is essential for the correct classification of G-NETs [38]. Interestingly, G-NETs of long-term proton pump inhibitor users are associated with less aggressive behavior (e.g., T1-T2 category, less often invasion of the serosa) and longer overall survival as compared to sporadic type 3 G-NETs, and may therefore be considered a separate subtype [39]. Previously categorized as type 3 G-NETs due to their lack of association with gastric atrophy or hereditary syndromes, G-NETs of long-term proton pump inhibitor users should be regarded similar to type 1 G-NETs, given their comparable etiology, including hypergastrinemia. G-NECs and G-MiNENs are occasionally referred to as type 4 G-NETs, though the use of this label is outdated as G-NECs and most G-MiNENs are poorly differentiated and by definition, not a NET. In most cases, G-MiNENs involve mixed adenocarcinoma-NECs, with mixed adenocarcinoma-NETs rarely being found [16].

Small Intestine

Small intestine-NENs (SI-NENs, siNENs), also referred to as small bowel-NENs (SB-NENs), are the most common type of NENs of the digestive tract in Western countries, with an incidence of 1.17–1.72 cases per 100,000 persons per year [1, 30, 31, 40]. Based on their location within the small intestine, SI-NENs are frequently categorized into duodenal-NENs, jejunal-NENs, and ileal-NENs. Of these, ileal-NENs comprise the largest group of SI-NENs, followed by duodenal-NENs, whereas jejunal-NENs are rare. In addition to CDX2, duodenal-NENs may express the site-specific transcription factors ISL1, PDX1, and ARX, which could be assessed by immunohistochemical stains [16]. The majority of SI-NENs involve small intestine-NETs (SI-NETs), with small intestine-NECs (SI-NECs) and small intestine-MiNENs (SI-MiNENs) being extremely rare. SI-NETs are the second most common type of NETs, following pulmonary NETs, and are the most common malignancy of the small intestine [1, 40–43]. Moreover, they are the most frequent source of metastatic NETs, being metastasized at the time of diagnosis in up to 73% of the patients, predominantly affecting the liver [3, 43–46]. The development of duodenal-NETs has been associated with MEN1 and neurofibromatosis type 1 (NF1), whereas jejunal- and ileal-NETs have been associated with germline variants of *MUTYH* [47–49], though the evidence remains contrasting [50]. Among the SI-NETs are the very rare composite gangliocytoma/neuroma and neuroendocrine tumors (CoGNETs), which were introduced in the WHO classification of 2022 and are mainly found in the duodenum [16]. CoGNETs were formerly known as gangliocytic paragangliomas, but as they are composed of three distinct cell types, including ganglion cells, spindle-shaped Schwann cells, and neuroendocrine epithelial cells, they are more correctly classified as composite tumors, consisting of ganglioneuroma with an epithelial (duodenal-)NET [16]. Though generally considered indolent tumors, any or all of the CoGNET components may occasionally metastasize to lymph nodes [16]. Among the SI-MiNENs are mixed adenocarcinoma-NECs and -NETs [16].

Appendix

Appendiceal-NENs (A-NENs, aNENs) have an annual incidence of 0.95–1.37 cases per 100,000 persons and mainly comprise the well-differentiated appendiceal-NETs (A-NETs), though appendiceal-NECs (A-NECs) and appendiceal-MiNENs (A-MiNENs) have also been reported [30, 31, 51–54]. A-NETs are generally considered sporadic, with up to 90% of A-NET being diagnosed histologically following routine appendectomies, performed for suspected appendicitis [55–57]. A-MiNENs exclusively comprise mixed adenocarcinoma-NECs [16]. Noteworthily, the very rare goblet cell carcinomas, initially known as goblet cell carcinoids, were frequently referred to as A-MiNENs as well. However, even though they do display neuroendocrine differentiation, they confer far more aggressive biology, show inconsistent immunohistochemical staining for neuroendocrine markers as well as a distinct mutational profile, and are not anymore classified as NENs [58–60]. Most likely, several aggressive A-MiNENs described in the past would now be reclassified as goblet cell carcinoma. The mix-up of appendix goblet cell carcinomas with A-NENs in literature has led to the misconception that A-NENs often have an unfavorable prognosis and that therefore the incidental finding of A-NENs should be followed by more extensive surgery, i.e., hemicolectomy. In contrast, A-NENs are among the NENs with the most favorable prognosis, and additional surgery is mostly not warranted [3]. A recent study by Nesti et al. [61] demonstrated that right-sided hemicolectomy following complete resection of A-NETs by appendectomy has no benefit on long-term survival.

Colorectum

Though classified as one entity by the WHO, colorectal-NENs (CR-NENs) can be split into colonic (C-NENs) and rectal-NENs (R-NENs) [62]. In Western countries, C-NENs and R-NENs have a relatively comparable incidence of 0.41–0.46 and 0.32–0.51 cases per 100,000 persons per year, respectively [30, 31]. However, in Asian countries, the annual incidence of R-NENs is higher, approaching 1.82 cases per 100,000 persons [63]. As a result, R-NENs are the most frequently observed type of NENs of the digestive tract in Asian countries, accounting for 53% of the cases [7, 63]. R-NENs essentially involve well-differentiated rectal-NETs (R-NETs) and are associated with a good prognosis. The latter association, however, may be confounded by the fact that R-NENs are regularly diagnosed incidentally during rectal examination or colonoscopy, and therefore are more commonly found in an early stage. Among R-NETs, those with low or absent chromogranin A were found to be associated with less aggressive clinical behavior and better prognosis compared to R-NETs that do express chromogranin A [64]. In contrast, C-NENs, which mainly comprise colonic-NECs (C-NECs) and colonic-MiNENs (C-MiNENs), are less frequently found by coincidence and are therefore often already metastasized at the time of diagnosis. Both C- and R-MiNENs involve mixed adenocarcinoma-NECs and mixed adenocarcinoma-NETs [16]. Though several CR-NENs have been reported in patients with familial colorectal cancer syndromes, including Lynch syndrome [65, 66] and familial adenomatous polyposis [67], the exact role of these syndromes in CR-NEN development remains to be elucidated.

Pancreas

Pancreatic-NENs (PanNENs, as used by the WHO), have an annual incidence of 0.8–0.94 cases per 100,000 persons, and are part of the GEP-NEN spectrum, though they generally are not considered as GI-NENs [30, 31]. Like the other GI-NENs, PanNENs include pancreatic-NETs (best abbreviated as PanNETs, as PNETs could also refer to the distinct primitive neuroectodermal tumors), pancreatic-NECs (PanNECs), and pancreatic-MiNENs (PanMiNENs). PanMiNENs are diverse and either involve mixed ductal adenocarcinoma-NECs/-NETs or mixed acinar carcinoma-NECs/-NETs [16]. Similar to duodenal-NENs, PanNENs may express the site-specific transcription factors ISL1, PDX1, and ARX. Moreover, loss of expression of ATRX and DAXX is indicative for PanNENs, yet could also be identified in other (metastatic) NENs, including pituitary NENs [16, 68]. PanNETs account for the majority of PanNEN cases [69, 70]. Though the majority of PanNETs are considered sporadic, they can be associated with MEN1 and to limited extents with Von Hippel-Lindau disease, NF1, and tuberous sclerosis [71]. Based on epigenetic and transcriptomic signatures, non-functioning PanNETs have been divided into three different subtypes. Subtype 1 has strong characteristics of alpha cells, and shows recurrent *MEN1* variants and limited copy number variants. Subtype 2 has less pronounced alpha cell characteristics as compared to subtype 1 and shows recurrent *MEN1*, *ATRX*, *DAXX*, and copy number variants. By contrast, subtype 3 resembles beta cells, lacks *MEN1, ATRX*, *DAXX,* and copy number variants, and has a favorable prognosis [16]. Functional, indolent PanNETs producing insulin also resemble the epigenetic signatures of beta cells and are characterized by *YY1* variants in 30% of the cases. Aggressive insulin-producing PanNETs, on the other hand, are more closely related to non-functioning PanNETs, showing recurrent *ATRX* and/or *DAXX* variants.

Extrahepatic Bile Ducts and Gallbladder

Extrahepatic bile duct-NENs (EHBD-NENs) and gallbladder-NENs (GB-NENs) are rare with an annual incidence of approximately 0.06 cases per 100,000 persons [31]. They develop sporadically and represent around 2% of all primary extrahepatic bile duct and gallbladder malignancies [72, 73]. NECs are more common than NETs in these sites and predominantly affect the gallbladder, followed by the common distal bile duct and common hepatic bile duct [74]. MiNENs may also develop in the extrahepatic bile duct and gallbladder and are either composed of an adenocarcinoma and a NEC or in rare instances of an adenocarcinoma, intracholecystic papillary neoplasm, and a NEC (mixed adenocarcinoma-intracholecystic papillary neoplasm-NECs) [16, 75–77] as of today.

Liver

Primary hepatic-NENs (H-NENs) develop sporadically and are extremely rare, accounting for only 0.3% of all NENs [78] and less than 1% of all primary neoplasms of the liver [79–83]. As the liver is the most frequently affected site of metastases from other (GEP-/GI-)NENs [84, 85], the distinction between primary H-NENs and metastases from other locations is important to establish correct treatment and prognosis of patients [74]. Immunohistochemical stains of site-specific transcription factors (e.g., CDX2, TTF1, ISL1, PDX1, ARX) and site-specific hormone production are helpful to identify the site of origin of NETs in the liver [16]. In contrast, distinguishing primary H-NECs from metastasized NECs is (nearly) impossible based on pathology and therefore requires clinical and radiological information [16, 74]. Primary H-NETs are slightly less common than primary H-NECs/H-MiNENs. H-NECs mainly include H-SC-NECs, though H-LC-NECs have also been reported [74]. H-NECs show a lower expression of cytokeratin and general neuroendocrine markers as compared to H-NETs and are consistently negative for HepPar-1 [74]. H-MiNENs are predominantly composed of mixed hepatocellular carcinoma and a NET/NEC, whereas mixed cholangiocarcinoma-NECs have also occasionally been described [16, 86].

Classification Based on Functionality

A third method of classifying NENs of the digestive tract is based on their functionality, with both functional-NENs (F-NENs) and non-functional-NENs (NF-NENs; shown in Fig. 1; Table 2). If combined with the other classifications, abbreviations used to describe the functionality are generally placed in front of both the location and WHO classifications (e.g., F-GEP-NENs, NF-GEP-NENs), though this strategy has not been acknowledged by the WHO.

Functional NETs of the Digestive Tract

F-NENs are characterized by their ability to secrete bioactive substances, such as hormones or peptides [87]. Some of them lead to well-established functional syndromes, which could be diagnosed based on the presence of functional symptoms. Hormone level assessment and immunohistochemical stains of site-specific hormone production may be performed for additional evidence [16]. Other F-NENs are rare, not frequently recognized, or exist only in theory.

To be able to produce hormones, F-NENs must either retain the biological activity of the neuroendocrine cells from which they originated (Table 4) or acquire the ability to ectopically/aberrantly produce hormones [7]. The latter may result in tumors secreting hormones that are normally not produced in the organ where the tumor is developing. For instance, F-PanNETs may (very rarely) produce adrenocorticotropic hormone (ACTH; ACTHoma) or growth hormone-releasing factor (GRF; GFRoma), which normally are produced in the pituitary and hypothalamus, respectively [88].

F-NENs mainly comprise the well-differentiated NETs and probably represent the gain of function variants in the tumor genome. Interestingly, to the best of our knowledge, no F-MiNEN of the digestive tract has been reported so far, even though they can be (partially) well-differentiated as well, according to the WHO classifications of 2017, 2019, and 2022.

Well-Established Functional Syndromes

Carcinoid Syndrome. Carcinoid syndrome occurs secondary to F-NETs that secrete various hormones and bioactive substances, such as serotonin, histamine, and bradykinin, into the circulation [89, 90]. It is characterized by flushing (60–85%), diarrhea (60–80%), abdominal pain (40%), facial telangiectasia (25%), and heart valve abnormalities (<20%; carcinoid heart disease) [91]. Carcinoid crisis, which is characterized by hypotension, arrhythmia, and bronchospasm, involves an extreme exacerbation of the symptoms and results from an excessive release of amines from the F-NET, which most commonly occurs during stressful situations (e.g., surgery, anesthesia, chemotherapy) [89]. F-NETs that cause the carcinoid syndrome were formerly referred to as "carcinoid" tumors, though the most

Table 4. Neuroendocrine cell types of the digestive tract[a]

Original cell type	Hormone	Location
α	Glucagon	Pancreas
β	Insulin	Pancreas
δ	Somatostatin	Stomach, small intestine, pancreas, appendix, colorectum
EC	Serotonin	Stomach, small intestine, pancreas, appendix, colorectum
ECL	Histamine	Stomach
G	Gastrin	Stomach, duodenum
I	CCK	Small intestine
K	GIP	Small intestine
L	GLP1, PPY	Small intestine, rectum
M	Motilin	Small intestine
N	Neurotensin	Small intestine
P/D1	Ghrelin	Stomach, small intestine, appendix, colon
PP	PP	Pancreas
S	Secretin	Small intestine, pancreas
VIP	VIP	Stomach, small intestine, pancreas, appendix, colorectum

CCK, cholecystokinin; EC(L), enterochromaffin(-like); GIP, gastric inhibitory peptide; GLP1, glucagon-like peptide 1; NEN, neuroendocrine neoplasm; PP, pancreatic polypeptide; PYY, peptide YY; VIP, vasoactive intestinal peptide. [a]This table is modified from the study by Kim et al. [7].

recent WHO classifications do not recommend the use of this term anymore for F-NETs of the digestive tract [16]. The incidence of carcinoid syndrome in general (also considering F-NETs outside the digestive system) is 1 case per 100,000 persons [92]. The prevalence of carcinoid syndrome among GEP-NENs is estimated to be 25%, primarily involving the ileum (rarely jejunum, duodenum, and pancreas) [93].

Gastrinoma. Gastrinomas secrete excessive amounts of gastrin, leading to a condition known as Zollinger-Ellison syndrome [94, 95]. Increased gastrin levels may cause hyperacidity, peptic ulcers, and diarrhea, among others. Gastrinomas are predominantly found in the duodenum (70%), pancreas (25%), and occasionally (5%) in other locations within the digestive tract [94]. The estimated annual incidence of gastrinomas is 0.5–3 cases per 1,000,000 persons [94, 96]. The majority of gastrinomas develop sporadically, yet in 20–30% of the cases, they are associated with MEN1 [94, 97].

Insulinoma. Insulinomas represent about 50–60% of the F-PanNETs and 1–2% of all pancreatic tumors [98, 99]. Insulinomas are typically solitary tumors of the pancreas that arise from the β cells of the islets of Langerhans and produce excessive amounts of insulin. This results in hypoglycemia and related symptoms such as confusion, dizziness, and fainting spells. The annual incidence is estimated to be 1–4 cases per 1,000,000 persons, with 4–8% of these cases being associated with MEN1 [98, 99]. Extra-pancreatic insulinomas are rarely described [100, 101].

Glucagonoma. Glucagonomas are tumors that secrete excessive amounts of glucagon, leading to a condition known as glucagonoma syndrome [102]. Symptoms include diabetes, weight loss, skin rash (necrolytic migratory erythema), diarrhea, and anemia. Glucagonomas are exclusively found in the pancreas, arising from the α cells of the islets of Langerhans [102]. They have an estimated annual incidence of 0.1–1 case per 1,000,000 persons [103], with less than 10% of the cases being associated with MEN1 [102].

VIPoma. VIPomas, also known as Verner-Morrison syndrome or pancreatic cholera syndrome, are NETs that secrete vasoactive intestinal peptides (VIPs) [104]. Excessive VIP production leads to profound diarrhea, hypokalemia, and dehydration. VIPomas are typically found in the pancreas (about 95%) and have an estimated annual incidence of 0.5–2 cases per 1,000,000 persons [88]. In 5% of the cases, VIPomas are part of MEN1 [104].

Rare/Theoretical Functional Syndromes

In addition to the well-established functional syndromes, several NETs that produce hormones lack a clearly defined clinical syndrome. For instance,

somatostatinomas are tumors that produce excess somatostatin, but as they are very rare (annual incidence of 1 in 40,000.000 million persons) and because the associated symptoms (e.g., abdominal pain, cholelithiasis, steatorrhea, symptoms of diabetes mellitus) are not frequently recognized, they are mainly discovered secondary to obstruction or during an endoscopy [105]. Similarly, PPomas, CCKomas, and secretinomas may produce excessive amounts of pancreatic polypeptide, CCK, and secretin, respectively, but are only described in a few case reports and, as a consequence, are not associated with a defined set of symptoms, nor are they acknowledged by the WHO [106–111]. Other potential F-NETs, such as motilinomas, histaminomas, neurotensinomas, GIPomas, GLP1omas, and PYYomas so far only exist in theory based on the presence of the respective neuroendocrine cells in the digestive tract, but lack any clinical evidence and are also not acknowledged by the WHO. In fact, most antibodies required for the identification of the respective cells are not available in pathology laboratories, and the respective hormones can only be measured in very few laboratories, making it difficult to distinguish "silent" hormone production in cells without hormone release from true F-NETs that do release hormones.

Nonfunctional NENs of the Digestive Tract

NF-NENs do not produce hormones, produce hormones at a low and asymptomatic level, or produce hormones that are not associated with any symptoms [87]. They, for example, lead to symptoms when they metastasize or exert a considerable mass effect, though other mechanisms exist as well, with NF-A-NENs, for example, causing symptoms by inducing appendicitis [112]. The majority of NECs and MiNENs are nonfunctional, while NF-NETs of the digestive tract are also relatively common [87, 113]. Of note, NENs progress regardless of their functional status. As such, both F- and NF-NETs of the digestive tract can acquire the ability to metastasize. As always, well-differentiated NETs, which are more likely to be functional than the poorly differentiated NECs, do have a better prognosis than poorly differentiated NECs [114].

Conclusion

NENs of the digestive tract comprise a highly diverse group of neoplasms with complex terminology. Although this review is not the first aiming to create awareness concerning the varying use of terminology in this field, previous reviews mainly focused on the WHO classification and did not consider the relation between the WHO classification and location- and functionality-based classifications [7, 9–11, 22, 33, 35]. We created an overview that combines these three types of classifications, taking into account the most recently used terminology. This overview is relevant when comparing previous literature using outdated classifications and could serve as guidance for writing future studies on NENs of the digestive tract, which are of high importance as the pathogenesis of a considerable group of NENs remains to be elucidated.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Noah C. Helderman: conceptualization, methodology, writing – original draft, writing – review and editing, and visualization; Manon Suerink, Gül Kilinç, and José G. van den Berg: writing – review and editing; Maartje Nielsen: conceptualization and writing – review and editing; and Margot E.T. Tesselaar: conceptualization, writing – original draft, and writing – review and editing.

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