The Problem of High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms

Well-Differentiated Neuroendocrine Tumors, Neuroendocrine Carcinomas, and Beyond

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KEYWORDS

• Neuroendocrine • Neoplasms • Carcinoma • Digestive • Gastroenteropancreatic • NET G3 • NEC

KEY POINTS

- Gastroenteropancreatic high-grade neuroendocrine neoplasms have 2 major subgroups: neuroendocrine tumors and neuroendocrine carcinoma.
- Diagnosis and treatment of high-grade gastroenteropancreatic neuroendocrine neoplasms is challenging owing to the lack of high-quality data.
- Diagnosis of high-grade gastroenteropancreatic neuroendocrine neoplasms depends on extensive pathology workup, including genetic data, because the morphologic criteria for defining well-differentiated versus poorly differentiated are not clear in all cases.
- Treatment of high-grade gastroenteropancreatic neuroendocrine neoplasms should separate between neuroendocrine tumors and neuroendocrine carcinoma and depends further on primary tumor site, stage, proliferation rate, and the clinical course.
- Future study reports on high-grade gastroenteropancreatic neuroendocrine neoplasms should give separate data for neuroendocrine carcinoma, neuroendocrine tumors, uncertain neuroendocrine neoplasms (uncertain differentiation), and mixed neuroendocrine-non-neuroendocrine neoplasm, as well as specifications of organ of origin, TNM and Ki-67.

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BACKGROUND

The 2010 World Health Organization (WHO) classification of gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) introduced morphology and grade with proliferation rate as the main determinant of NEN behavior. It defined NEN as either well-differentiated low-grade (G1-G2) neuroendocrine tumors (NET) or poorly differentiated high-grade (G3) neuroendocrine carcinomas (NEC).[1] The 2017 WHO classification of pancreatic NETs defined a new group of well-differentiated G3 pancreatic tumors (NET G3).[2] The NET category is now only used for well-differentiated tumors regardless of their proliferation index (G1-G3), whereas the NEC category is used for poorly differentiated G3 NEC. The terminology of NEN G3 relates to all G3 (Ki-67 >20%) neuroendocrine malignancies; that is, both NET G3 and NEC (**Table 1**). The separation of NET G3 and NEC depends on the different genetic backgrounds of the 2 groups and resulting different biology. NET G3 has been formally only been implemented for pancreatic NEN; however, an expansion to other GEP NEN entities seems likely. Although the WHO classification for NEN G3 has been validated for its prognostic relevance, several problems remain and different morphologic, molecular, clinical, and prognostic entities were recently highlighted.[3–8] The robustness of histomorphologic criteria for defining well-differentiated versus poorly differentiated is questioned even among expert pathologists. Finally, its relevance for predictive benefits of therapy is even more problematic, although lower response rates to cisplatin-based chemotherapy in NETG3 was evident very early.[9,10] Currently, the NEN G3 category has been considered a single entity in most studies, making a final understanding of the benefit of various therapeutic options for NET or NEC category of patients uncertain. In this article, we address the problem of how to diagnose and treat GEP NEN G3, with a specific focus on NET G3 versus NEC, and we propose a new NEN G3 category.

DIAGNOSING WELL-DIFFERENTIATED NEUROENDOCRINE NEOPLASMS: FROM A SINGLE ENTITY TO A HIGH-GRADE NEUROENDOCRINE TUMOR OR NEUROENDOCRINE CARCINOMA CATEGORIZATION

Epidemiology, and Diagnostic and Prognostic Characteristics

Epidemiologic data on NET G3 compared with NEC are very scarce, and the numbers of NET G3 cases reported in studies are very few. Both NET G3 and NEC are more common in male patients. The main primary tumor sites in NEC are quite similar, distributed between the colon, rectum, pancreas, stomach, and esophagus.[11–14] In contrast, NET G3 are mainly located in the pancreas, with other primary sites of like

Table 1
Nomenclature for GEP NEN G3

	Used for	
NEN G3	Addressing both NET G3 and NEC	If differentiation is uncertain
NET G3	Well-differentiated, Ki-67 >20%	
NEC	Poorly differentiated, Ki-67 >20%	
MiNEN	Neoplasms with both >30% neuroendocrine and gland-forming component	

Abbreviations: G3, high grade; GEP, gastroenteropancreatic; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEN, neuroendocrine neoplasm.

Data from Klöppel G, Couvelard A, Hruban RH, et al. Introduction to chapter 6 neoplasms of the neuroendocrine pancreas. In: Lloyd RV, Osamura RY, Klöppel G, et al, editors. WHO classification of tumors of endocrine organs. 4th edition. Lyon (France): IARC; 2017. p. 211–4.