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Neuroendocrine tumor G3 of bronchopulmonary origin and its classification

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Abstract
Neuroendocrine tumors (NET) with high proliferative activity (Ki-67 index >20% and/or mitotic counts $>2\,mm^2$) are defined as NET G3 in the 2019 World Health Organization (WHO) classification of digestive system neuroendocrine neoplasms (NENs). NETs G3 occur mostly in the pancreas, colon, rectum, and stomach and only rarely in the small intestine and the appendix. In the bronchopulmonary system, similar tumors have also been recognized and were mostly classified as atypical carcinoid (AC) or large cell neuroendocrine carcinoma. Bronchopulmonary NENs that were classified as NETs G3 are characterized by histological and immuno-histochemical similarities with carcinoids/NETs, and a clinical course that is more aggressive than with ACs and similar to that of neuroendocrine carcinomas. The morphomolecular and clinical features of bronchopulmonary neoplasms with a high proliferative activity were reviewed and a future classification system that is applicable for both digestive and bronchopulmonary NETs is proposed.

KEYWORDS
classification, Ki-67, lung neuroendocrine neoplasms, NET G3

INTRODUCTION

Neuroendocrine neoplasms (NENs) which arise from the bronchopulmonary (BP) and gastroenteropancreatic (GEP) systems account for over 90% of all NENs.[1] The BP- and GEP-NENs as well as the remaining NENs of the body share a morphomolecular, hormonal and prognostic dichotomy with the separation into two histological subtypes: the neuroendocrine tumor (NET) and the neuroendocrine carcinoma (NEC). Since the two subtypes are treated differently, their accurate diagnosis is of great clinical importance. The World Health Organization (WHO) classifications for BP- and GEP-NENs differ, however, in terminology and grading systems.[2,3] In 2018, a uniform classification framework of NENs was proposed by the WHO experts of different organ fields.[4] This proposal largely reduced inconsistencies among different classification systems by equating typical (TC) and atypical carcinoids (AC) of BP-organs with the NETs G1 and G2 of the GEP-organs. One of the remaining issues in this proposal is the diagnostic and clinical handling of NENs in the BP-system corresponding to G3 GEP NETs. This review focuses on the characterization of the high-grade BP-carcinoids that correspond to "NETs G3" and discusses the cross-organ classification for NENs that better reflects clinical and prognostic characteristics of the patients with BP-NENs.

Abbreviations: AC, atypical carcinoid; BP, bronchopulmonary; GEP, gastroenteropancreatic; LCNEC, large cell neuroendocrine carcinoma; NGS, next generation sequencing; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumors; TC, typical carcinoid; WHO, World Health Organization.

CHRONOLOGY OF DESCRIPTIONS, TERMS, AND CLASSIFICATION

The first descriptions of the cells and the resulting tumors, which we summarize today under the terms neuroendocrine cell system and neuroendocrine neoplasms, were made at the end of the 19th and beginning of the 20th century. In connection with the further development of the microscope and the introduction of special staining techniques, Langerhans described the islet cells in the pancreas in 1869, while Heidenhain in 1870 and Kulchitsky in 1897 described the gastrointestinal neuroendocrine cells, although no statement was yet possible on the function of these cells.[5,6] Indications of the hormonal nature of the described cells only emerged from the epoch-making work of Mering and Minkowski (1889), Edward Sharpey-Schäfer (1895), Bayliss and Starling, and Banting and Best (1922).[7-10] Among the first and most important describers of tumors that originated from the neuroendocrine cells of the pancreas and the gastrointestinal system are Nicholls (1902) and Warren (1926) for the islet cell tumors,[11,12] and Lubarsch (1888), Ransom (1890), Oberndorfer (1907), and Gosset and Masson (1914) for the intestinal tumors.[6,13-17] Shortly thereafter, the hormonal syndromes (i.e., hyperinsulinemic hypoglycemia and carcinoid syndrome) associated with these tumors were reported.[6,18-20]

The German pathologist Siegfried Oberndorfer coined the term "carcinoid" (carcinoma-like) when he described a group of small ileal tumors that were similar to carcinomas but behaved differently.[14] Originally, Oberndorfer thought the carcinoids growth was infiltrative but did not metastasize. However, it was soon shown that carcinoids were able to metastasize, and in 1929 Oberndorfer acknowledged the metastatic potential of carcinoids, when he presented a series of 36 carcinoids of the ileum and appendix.[6,21] In the 1930s carcinoids were increasingly identified in various sites, mostly in the intestine, including rectum, appendix, stomach, and Meckel's diverticulum, but also in nonintestinal organs, such as the ovary.[6] The first bronchopulmonary tumor which likely represents a carcinoid, was detected by bronchoscopy as an endobronchial tumor. It was described by Jackson in 1917, and introduced and named as "endothelioma of the bronchus".[22] In 1937, Herwig Hamperl reported nine benign bronchial neoplasms including seven that were histologically comparable to intestinal carcinoids and introduced as "benign bronchial carcinoids."[23] As with the intestinal carcinoids, the metastatic potential of the bronchial carcinoids soon became known.[24] In 1961, Goodner reported a high rate of metastasis (44%) and a low 5-year disease-free rate (33%) in a series of 27 patients with BP-carcinoids.[25] In 1972, Arrigoni described the histological features of BP- carcinoids with aggressive clinical course. Bronchial carcinoids with frequent mitotic figures, pleomorphisms, a high cellularity and/or presence of necrosis were shown to be associated with distant metastases in over 70% of cases, and the term AC was introduced.[26]

In 1963 Williams and Sandler proposed the first classification for carcinoids, based on anatomical location and embryological origin. Foregut, midgut, and hindgut carcinoids were distinguished and related to the carcinoid syndrome.[27] In 1980, the term carcinoid was applied to the intestinal, bronchopulmonary, and urogenital tumors in the first WHO classifications, highlighting that all carcinoids should be regarded as malignant tumors.[28] In the pancreas, the term "islet cell tumor" included islet cell adenoma and islet cell carcinoma.[28] After 1990, the term carcinoid had become more and more inappropriate to encompass all NENs due to the increasing knowledge on the morphological heterogeneity of neoplasms with neuroendocrine differentiation, due to the uncertainty whether the carcinoid syndrome relates only to a special type of carcinoid or to all carcinoids, and due to the uncertain malignant potential of the various carcinoids.[29] In 2000, the second edition of the WHO classification for endocrine tumors introduced the new terms well-differentiated endocrine tumor and well-differentiated endocrine carcinoma based on the metastatic and infiltrative status of the neoplasms.[30] However, the 1999 WHO classification for lung and thoracic organs divided the carcinoids into typical and atypical, and all the subsequent editions published in 2004, 2015, and 2021 retained this terminology.[31–33] The 2010 WHO classification for NENs of digestive organs introduced a new system for dividing NENs. Well-differentiated NENs were called NETs and graded into NET G1 and NET G2 according to their proliferative activity determined by Ki-67 index and mitotic counts, and compared to NECs G3 with Ki-67 index >20% or mitotic counts >20 per 2 mm^2.[34] In the 2017 WHO classification for the endocrine pancreas, the NET grading system was extended to a group of NET G3 characterized by a high Ki-67 index >20% and/or mitotic counts >20 per 2 mm^2.[35] In the 2019 WHO classification of digestive system NENs, the pancreatic three-tiered NET G1, G2, and G3 grading was applied to all digestive system NENs including the hepatobiliary organs[2] (Table 1).

STATUS QUO IN THE 2021 WHO CLASSIFICATION OF BP-NENS

The BP-carcinoids (also called synonymously neuroendocrine tumors) are defined as malignant neuroendocrine neoplasms with a well-differentiated organoid architecture and are divided into typical and atypical forms (TC and AC on the basis of the number of

TABLE 1 WHO classifications of neuroendocrine neoplasms of bronchopulmonary (BP) and gastroenteropancreatic neuroendocrine neoplasms (BP-NEN WHO 2021 and GEP-NEN WHO 2019)

| Differentiation | BP-NEN | | | | GEP-NEN | | |
	Terminology	Mitoses per 2 mm^2	Necrosis	Ki-67 index*	Terminology	Mitoses per 2 mm^2	Ki-67 index
Well-differentiated	TC	0–1	No	Up to 5%	NET G1	<2	<3%
	AC	2–10	Focal, if any	Up to 30%	NET G2	2–20	3%–20%
					NET G3	>20	>20%
Poorly differentiated	LCNEC	>10	Yes	40%–80%	Large cell type (LCNEC)	>20	>20%
	SCLC	>10	Yes	50%–100%	Small cell type (SCNEC)	>20	>20%
Mixed NEN and non-NEN neoplasms	Combined SCLC/LCNEC**				MiNEN***		

Note: Table modified from references.[2,3]

Abbreviations: AC, atypical carcinoid; BP, bronchopulmonary; GEP, gastroenteropancreatic; LCNEC, large cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine and nonneuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SCLC, small cell lung carcinoma; TC, typical carcinoid.

*Not included in criteria.

**Amount of the non-NEN components is not defined.

***Each component accounts for at least 30% of total tumor cell population.

mitoses:TC <2 mitoses per 2 mm^2 and absence of necrosiscc; AC 2–10 mitoses per 2 mm^2 or presence of necrosis).[3] This classification seems simple, but it has its pitfalls. Particularly problematic is that BP-NETs may have a mitotic count >10 in 2 mm^2. These values overlap with the proliferative activity in NECs with the result that the BP-NETs >10 mitoses are classified as large cell NECs due to their nonsmall cell cytology. The tumors with more than 10 mitoses and/or >30% Ki-67, which received in the WHO classification the annotation "generally corresponding to pancreatic NET G3,"[3] were, however, not included in the definition of atypical BP-carcinoids[3] (Table 1).

The role of Ki-67 in the diagnosis of BP-NENs is critically discussed and eloquently commented on in the 2021 WHO classification. On the one hand, the determination of the Ki-67 index is considered to be of value in the diagnostic and prognostic differentiation between NET and NEC.[31] On the other hand, the use of Ki-67 in diagnosing BP-NETs is discouraged for methodological reasons related in particular to the different cut-off values in the various studies that are available so far.[36-45] This controversial statement finds expression in the controversial sentence: "Although in general Ki-67 correlates with prognosis in surgically resected lung NENs, unlike in gastrointestinal and pancreatic NENs, data have not consistently supported a primary role for Ki-67 in diagnosis and classification for the following reasons".[31] However, it is acknowledged that Ki-67 has a value in small biopsies, where the morphological distinction between NET and NEC, based on mitotic counts is difficult because of small

sample size and crush artifacts. Ki-67 is also useful for the separation of NET and NEC in metastatic carcinoids. In the metastatic setting, it is, in addition, recommended to use the term "metastatic carcinoid NOS" instead of classifying into TC or AC.[31,44] However, the use of "metastatic carcinoid NOS" is ambiguous in cases in which the proliferative activity exceeds 10 mitoses per 2 mm^2 or 30% Ki-67, since these threshold values define the large cell neuroendocrine carcinoma (LCNEC) in the WHO 2021 for thoracic organs.

The most recent WHO classification for endocrine organs published in 2022 encompasses NENs of both pancreatic and nonpancreatic organs (i.e., bronchopulmonary, skin, genitourinary organs, and breast) and recommends evaluating the Ki-67 index for all NENs.[46] However, this recommendation does not offer an adequate diagnostic position for BP-NETs G3 (nor for thymic carcinoids) and only cryptically notes that high-grade BP- and thymic NETs are considered large cell NECs.[46]

The Ki-67 index counted in at least 500 tumor cells and a mitotic count counted in a 2 mm^2 are both indices of cell cycle activity, which naturally correlate with each other. However, the former is higher than the latter on average fourfold, because the mitotic figure reflects only the mitotic phase of the proliferating cell, while the nuclear protein, represented by the Ki-67 antigen, is active in the G1, S, G2, and M phases of the cell cycle.[45] The enormous disparity between mitotic counts and Ki-67 numbers in NETs in fact highlights the poorer capability to determine the tumors'

TABLE 2 Bronchopulmonary neuroendocrine tumors with a proliferative activity exceeding either Ki-67 index 20% and/or mitotic count more than 10

Citation	Definition	Total	Female	Age mean (range)	Nonsmoker**	Proposed terminology	TP53 alteration/ overexpression	Rb1 alteration/ protein loss
Cros et al.[50]	Mitosis >10, Ki-67 >20%	11	7/11	60	7/11	High grade NET	2	1
Sazonova et al.[56]	Mitotis 10–30	4	3/4	59	4/4	Carcinoid with increased mitotic count	0/4	0/4
Hermans et al.[52]	Mitosis >10, Ki-67 >20%	7	3/7	59	1/6	NEN with well-diff. morphology	2/6	3/7
Oka et al.[45], Kasajima et al.[42]	Mitosis >20, Ki-67 >20%	30	12/30	65	5/10	NET G3	0/21	1/22
Rehkmann et al.[44]	Mitosis >20, Ki-67 >20%	28	18/28	61	18/28	Metastatic carcinoid	0/9	0/19
Quinn et al.[53]	Mitosis >10	12	5/12	65	4/12	NET G3	ND	ND
Rehkmann et al.[55]	Mitosis >10	2	ND	ND	ND	Carcinoid-like LCNEC	0	0
Inafuku et al.[51]	Mitosis >10	2	2/2	77	2/2	NET G3	ND	ND
Volayoudom-Cephise et al.[54]	Mitosis >20, Ki-67 >20%	1	ND	ND	ND	NET G3	ND	ND
Total N (%)		93	50/94 (53%)	63 (27–88)	41/73 (56%)		2/48 (4%)	2/57 (4%)

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; ND, no data available; NET, neuroendocrine tumor.
*Seven patients from Kasajima et al.[42] are included in Oka et al.[45]
**Including nonactive smoker or ex-smoker.

proliferative activity by counting mitoses than by counting Ki-67 labeled cells. This numerical difference explains the small, but prognostically important, discordance between TC and NET G1. We were able to show that 13% of TCs corresponded to NET G2, and that these patients had a significantly worse outcome than the TC/NET G1 patients, suggesting that a grading based on mitotic counts alone may underestimate patients' outcome.[45]

BRONCHOPULMONARY "NET G3"

In the 2019 WHO classification for digestive tumors, NET G3 is uniformly defined for all digestive organs.[2] For BP-NENs, as criticized by the 2021 WHO classification for thoracic organs, no uniform Ki-67 based grading exists,[31] although several studies have been reported between 2001 and 2019.[31,36–45,47] We applied the grading system of the 2019 WHO classification for digestive tumors to a series of 257 surgically resected primary BP-NENs to determine how frequently NET G3 is represented and to identify the prognostic significance of this tumor category. BP-NETs G3 represented 4% of all BP-NENs and 14% of all BP-NETs.[45] These data are slightly higher than that in the pancreas.[48] Interestingly, Rekhtman et al. reported an increasing incidence of BP-NENs with carcinoid-like morphology and Ki-67 above 20% from 13% in primaries up to 27% in metastases.[44]

Although rare, the lungs seem to belong to the common sites of origin of NETs G3 in the body. In a series of 130 NETs G3 including both primary and metastatic tumors, lung was second in frequency (20%) after pancreas (42%).[49]

The outcome of the patients was significantly poorer than that of patients with NET G1 and NET G2 and overlapped with that of NEC patients. However, the 2-year disease free survival rate of the NET G3 patients was higher than that of NEC patients (75% vs. 45%).[45] These data are comparable to the results from a large series in pancreatic NEN patients.[48]

When the literature is searched for BP-NETs with proliferation activity greater than 20% Ki-67 index and/ or mitotic count >10, ten studies are found, including ours, reporting 93 cases.[42,44,45,50–56] In these studies, the tumors were given different names, such as high-grade NET, carcinoid-like LCNEC, or finally NET G3 (Table 2). Besides the high proliferative activity, all presented a well-differentiated histology in common. Compared with NEC patients (mean age 68, women 13%, nonsmokers 5%),[42] younger patients (mean age 63), women (53%), and nonsmokers (57%) were affected[45,50] (Table 3).

Histologically, the BP-NETs G3 of our study showed mixed diffuse and organoid patterns with focal spindle-cell cytology, salt and pepper chromatin pattern and occasional nuclear pleomorphism[42] (Figure 1). Immunohistochemically, the BP-NETs G3 were characterized by normal p53 (100%) and normal Rb1 expression (95%), which contrasted with the data in BP-NECs (abnormal p53 and Rb1 in 50% and 74%, respectively).[45,49]

So far there are no molecular studies in BP-NENs defined as BP-NET G3. However, there are three studies, in which the examined tumors, or a fraction of them, probably correspond to BP-NET G3. In the study by Cros et al., which is included in Table 2, seven of 11 tumors showed a loss of the chromosomal region 11q13 containing the *MEN1* gene, which is known to be more frequent in ACs than in TCs[57,58] and is extremely rare in NECs.[55,57] Targeted next generation sequencing (NGS) showed recurrent mutations in *TP53, ATM, PTEN, RAD50* and *TSC* in two of seven cases.[50] Using NGS Simbolo et al. separated three clusters of BP-NENs on the bases of the most common mutations. The first cluster included

TABLE 3 Helpful clinicopatholgic features for the differenatial diagnosis of bronchopulmonary NET G3 versus NEC

	NET G3	NEC
Age	Mean 63	Mean 68
Sex	Female > male	Male » female
Association with smoking	Low	High
Histology	Well-differentiated	Poorly differentiated
Immunohistochemistry	Usually normal p53 and normal Rb1	Frequent abnormal p53, abnormal Rb1
Genomic profiles	Frequent $MEN1^{mut}$, rare *TP53* alteration	Frequent *TP53, RB1* alteration
Outcome	Poor	Poor
Prognostic factor	Unknown (Rb1?)	TNM-Stage

Abbreviations: NEC neuroendocrine carcinoma; NET, neuroendocrine tumor.
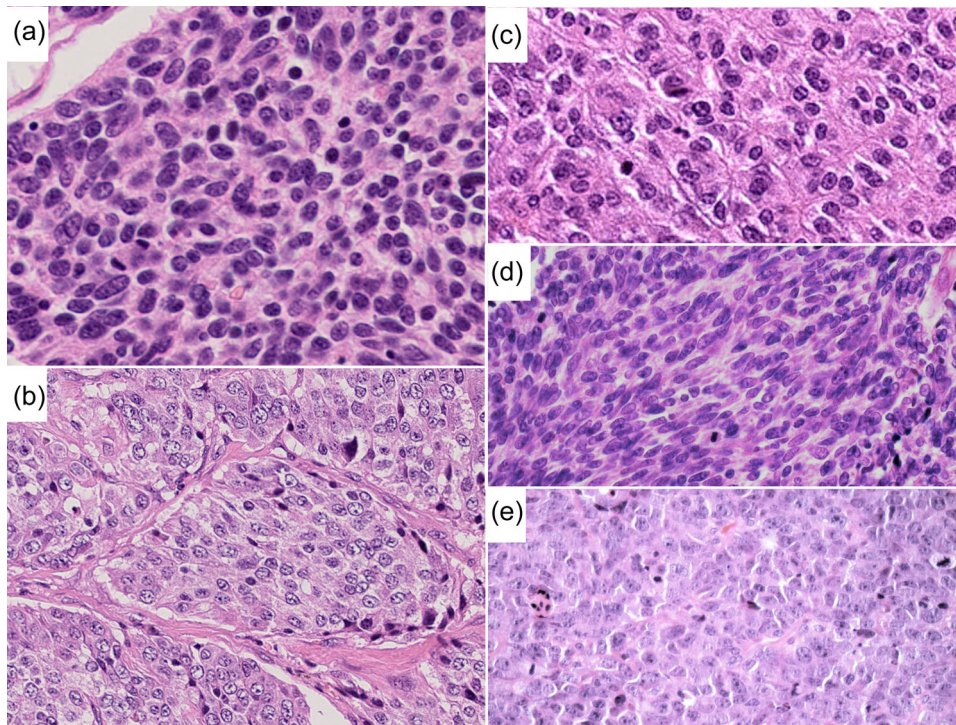*Source*: 42, 44, 45, 50–56.

FIGURE 1 Histological nuclear features of bronchopulmonary (BP) neuroendocrine tumor G3 (NET G3; a,b) compared to BP-NET G2 (c) and BP-neuroendocrine carcinoma (NEC), small (d) and large cell (e) type

ACs characterized by mutated MEN1 and wild type TP53 and Rb1. The second cluster included LCNECs showing mutated TP53 and Rb1 and wild-type MEN1. The third cluster was characterized by mutations in *TP53* (41%), *MEN1* (23%), and *RB1* (18%).[59] The patients in the latter cluster had a clinical course in-between of the other clusters.[59] Similar data were reported in six BP-NENs by Alcala et al., which were called "supra-carcinoids".[60]

Data regarding treatment of BP-NETs G3 are still limited. In a series of seven surgically resected patients, four patients received a cisplatin-based postoperative chemotherapy.[42] In the other series with 11 patients, four received a cisplatin-based chemotherapy and two somatostatin-analog therapy.[50] So far data regarding therapy response for NETs G3 are limited. Platinum based chemotherapy seems to be not effective, while response to capecitabine and temozolomide was reported in two of three cases.[53]

CONCLUSION

Evidence is accumulating that the category of NET G3 that has been defined in the NENs of the digestive system can also be identified in the lung. Since the morphological and clinical features of BP-NET G3 are comparable to those of NETs G3 in other organs, a common classification and grading are conceivable and should be realized in a future WHO classification. This would facilitate comparability of morphogenetic studies and treatment options in NENs including BP-NENs.

CONFLICT OF INTEREST

None declared.

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