ORIGINAL ARTICLE

Well-Differentiated Bronchopulmonary Neuroendocrine Tumors: More Than One Entity

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ABSTRACT

Introduction: Until now, well-differentiated bronchopulmonary neuroendocrine tumors (bpNET) occurring either sporadically (sp-bpNET) or in the context of multiple endocrine neoplasia type 1 (MEN1) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) are regarded as similar entities. However, in contrast to sp-bpNET: MEN1-related and DIPNECH-related bpNET rarely metastasize or lead to bpNET-related death. We aimed to describe and compare the course of the disease of sp-bpNET, DIPNECH- and MEN1-related bpNET.

Methods: All patients with histologically confirmed MEN1-related bpNET from the DutchMEN Study Group database (1990-2017), patients with resected sp-bpNET and DIPNECH patients referred to a Dutch European Neuroendocrine Tumor Society center between 2000 and 2018 were included. Fisher's exact test was used for comparison between groups. The primary end point was disease-specific mortality (DSM). Kaplan-Meier and log-rank test were used to compare survival. Cox regression was used to identify risk factors for DSM in the sp-bpNET subgroup.

Results: We included 112 sp-bpNET, 29 MEN1, and 27 DIPNECH patients. Tumor classification was similar across subgroups. A total of 20 patients (18%) with sp-bpNET died because of bpNET, compared with none in the MEN1 group and DIPNECH group. Median disease-specific survival was 12.3 (confidence interval: 6.3–18.3) years for patients with sp-bpNET, and not estimable for the other subgroups ($p < 0.001$). Differences in baseline characteristics did not explain worse survival in sp-bpNET. Tumor classification and age at diagnosis were independent risk factors for DSM in sp-bpNET.

Conclusions: Patients with sp-bpNET have a significantly higher DSM compared with MEN1 or DIPNECH-related bpNET, unexplained by differences in baseline characteristics. This implies that not all bpNET are similar entities.

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[#]See Appendix.

Drs. van den Broek and Levy contributed equally to this work.

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Introduction

Bronchopulmonary neuroendocrine neoplasms comprise a heterogeneous group of malignancies of the lung, originating from neuroendocrine cells. These neoplasms can be classified as bronchopulmonary neuroendocrine tumors (bpNET), with a subdivision in typical carcinoid (TC) and atypical carcinoid (AC); SCLC or large cell neuroendocrine carcinoma (LCNEC). All these tumors have been grouped under "bpNET" in the most recent WHO Classification of Lung Tumors in 2015.[1] Classification is based on histopathological features, including mitotic count, the presence or absence of necrosis and a variety of cytologic and morphologic features.[1] TCs and ACs—historically called "carcinoid"—account for 1% to 2% of all lung malignancies and are considered well-differentiated tumors with an overall favorable course.[2] Although grouped together with the poorly differentiated SCLC and LCNEC, the 2015 WHO classification recognizes the evident major clinical, epidemiologic, histologic and genetic differences between lung carcinoids and the high-grade SCLC and LCNEC.[1] For the purpose of this article, we consider only the well-differentiated typical and ACs of the lung, which we will refer to as bpNET. bpNET arise sporadically (sp-bpNET) or in the context of a hereditary predisposition, for example, multiple endocrine neoplasia type 1 (MEN1). Another context in which bpNET may arise, is diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), a proliferation of neuroendocrine cells.

Most bpNET develop sporadically. sp-bpNET are classically diagnosed in the fifth and sixth decade of life, and prognosis largely depends on histologic subtype: reported 5-year survival rates are 87% to 94% and 44% to 80% for TC and AC, respectively.[3,6] Furthermore, lymph node metastases, distant metastases and higher proliferation rate have been identified as adverse prognostic factors.[5,7]

MEN1 is a rare hereditary disease predisposing patients to the development of several endocrine tumors. The classic manifestations of MEN1 are parathyroid hyperplasia or adenomas, neuroendocrine tumors of the pancreas and duodenum and pituitary adenomas, which are caused by inactivation of the *MEN1* gene.[8] Next to other manifestations as gastric- and thymic NET, adrenal tumors and breast cancer, patients are also at risk of developing bpNET with a prevalence of 4.7% to 6.6% of MEN1 patients.[9-14] Clinical practice guidelines advise frequent thoracic imaging to detect and monitor these tumors. However, more recent studies have shown that MEN1-associated bpNET seem to have an indolent behavior and do not decrease overall survival in MEN1 patients, although a few aggressive cases with fatal outcome have been described.[11,12] Curative surgery is considered the first treatment of choice, but a watch-and-wait policy is suggested for small (<2 cm) and slow-growing MEN1-related bpNET.[15,16]

DIPNECH, an uncommon pulmonary disease characterized by proliferation of pulmonary neuroendocrine cells restricted to the bronchial and bronchiolar epithelium and presence of tumorlets, is recognized by the WHO as a preinvasive precursor lesion for bpNET.[1] This condition typically occurs in nonsmoking, middle-aged women and may cause a variety of symptoms (e.g., cough, dyspnea, wheezing) for which the term "DIPNECH syndrome" has been coined.[17,18] Although the diagnosis of DIPNECH is currently not defined by stringent clinic-pathologic and radiologic criteria, Rossi et al.[18] have proposed a comprehensive flowchart for the diagnosis of either solely DIPNECH, or DIPNECH syndrome. In most patients, DIPNECH is associated with a stable or slowly locally progressive disease, with only a few disease-related deaths reported to date.[19-24]

Until now, bpNET of any type are considered the same disease, which is also reflected in the recently updated international guidelines.[25,26] However, on the basis of clinical experience and earlier reports on the natural course of sp-bpNET, MEN1-related bpNET and DIPNECH-related bpNET, the question arises whether these subtypes are in fact different entities; MEN1- and DIPNECH-related bpNET rarely metastasize or lead to bpNET-related death,[9-13,19-24] while the prognosis of sp-bpNET seems more heterogeneous—and perhaps worse than nonsporadic forms of bpNET.[3-7]

To our knowledge, head-to-head comparisons between sp-bpNET, MEN1-related bpNET and DIPNECH-related bpNET are lacking to date. Therefore, in this cohort study, we aimed to compare disease-specific mortality (DSM) of patients with sp-bpNET, MEN1- and DIPNECH-related bpNET. In addition, because we describe a rather large cohort of sp-bpNET, we aimed to identify independent risk factors for DSM in patients with sp-bpNET.

Materials and Methods

Study Design and Patients

All patients with sp-bpNET referred to the Netherlands Cancer Institute (NKI) and University Medical Center Utrecht (UMCU) European Neuroendocrine Tumor Society Center of Excellence (ENETS CoE) between 2000 and 2019 who had undergone surgery with curative intent were included. Similarly, all patients with histopathologically confirmed bpNET in the context of DIPNECH referred to this ENETS CoE within the same time period were included. Patients were considered to have DIPNECH or DIPNECH syndrome on the basis of the diagnostic flowchart that has been developed by Rossi et al.,[18] taking into account symptoms and lung function abnormalities, compatible radiological signs and histologic features.[16] Patients with bpNET in the context of DIPNECH and DIPNECH syndrome were grouped in one subgroup and further named "DIPNECH."

Patients with bpNET in the context of MEN1 were all selected from the Dutch national MEN1 database of the DutchMEN Study Group (DMSG). This database covers over 90% of the adult Dutch MEN1 population and includes all MEN1 patients more than or equal to 16 years of age at the end of 2017, under treatment at one of the Dutch university medical centers between 1990 and 2017. Detailed information on the DMSG database methods have been described previously.[27] To avoid misclassification of lung metastasis from NET of a different origin in patients with MEN1, only patients with histopathologically confirmed bpNET were selected for analysis.

Patient and tumor characteristics were retrieved from the longitudinal institutional neuroendocrine neoplasia database, in which all patients treated in the joint center are included, and the DMSG database. Tumor staging at time of diagnosis was based on pathologic reports and derived from the eighth edition of the TNM staging for NSCLC, which is also used for bpNET.[28] Because no consensus exists on TNM staging for DIPNECH, this was not performed for the DIPNECH cohort. Tumor grading in typical and AC was based on mitotic count and the presence of necrosis. Ki67-index was also included in the analysis. When unusually high or low mitotic count or Ki67-index were found, consensus on typical or atypical classification was reached within a multidisciplinary tumor board, on the basis of a combination of tumor cell shape, structure, form and size and the dis- or concordance of mitotic count and Ki67-index.

This study was conducted in agreement with the NKI and UMCU ethical guidelines and all patients gave consent for the use of their medical data as per institutional protocol.

Outcomes

For the three subgroups, primary outcome was disease-specific mortality. Secondary outcomes were identification of differences in patient characteristics between the subgroups that could influence survival. For patients with sp-bpNET, identification of independent risk factors for DSM was an additional outcome.

Statistics

Median with (interquartile) range (IQR) was used to describe continuous variables, frequency and percentages were calculated for categorical variables. For comparison between groups Fisher's exact test was performed for categorical variables, and the Wilcoxon ranked sum test for continuous variables. DSM was defined as bpNET-related death. Patients who died of unknown causes were considered to have died of bpNET if recurrence or metastatic disease was present at last follow-up. Patients with no evidence of disease and death less than or equal to 6 months after last follow-up were considered to have died of other causes. Patients who died of other causes or were alive at end of follow-up were censored. For visualization and comparison of survival between subgroups Kaplan-Meier curves and the logrank test was used, respectively. Cox regression was performed for univariable and multivariable analysis of risk factors for DSM. Analysis were performed using IBM Statistical Package for the Social Sciences Statistics software, version 25.0, and R version 3.6.2, package "survival".

Results

Patients

A total of 168 patients were included, of which 112 were patients with sp-bpNET, 29 patients had histologically proven bpNET in the context of MEN1, and 27 patients had a bpNET in the context of DIPNECH. Baseline characteristics and comparisons for all three subgroups can be found in Table 1. Because pathologic characteristics are inherently associated with tumor classification, these were stratified according to typical and AC classification, and can be found in Table 2.

Survival

Median follow-up for all patients was 4.8 years (IQR: 2.2–7.5). For patients with sp-bpNET, this was 4.4 years (IQR: 2.0–7.2), for patients with MEN1-related bpNET this was 6.7 years (IQR: 4.9–12.0) and for patients with DIPNECH median follow-up was 2.9 years (IQR: 1.3–6.7). A total of 20 patients (17.8%)

Table 1. Baseline Characteristics for the Three Subgroups

Characteristics, N (%)/Median (Range)	Sporadic bpNET	MEN1	Sporadic vs. MEN1 *p*-Value	DIPNECH	Sporadic vs. DIPNECH *p*-Value	MEN1 vs. DIPNECH *p*-Value
Total	112	29		27		
Age at diagnosis	54 (18-76)	44 (23-66)	0.008	63 (34-85)	0.004	<0.001
Sex			0.671		<0.001	0.001
Male	46 (41.1)	10 (34.5)		0		
Female	66 (58.9)	19 (65.5)		27 (100)		
WHO PS			n/a		0.351	n/a
0	45 (40.2)			8 (29.6)		
1	45 (40.2)			16 (59.3)		
2	2 (1.8)			0		
Unknown	20 (17.9)			3 (11.1)		
Tumor classification			0.863		0.096	0.209
Typical	73 (65.2)	20 (69.0)		23 (85.2)		
Atypical	38 (33.9)	9 (31.0)		4 (14.8)		
Unknown	1 (0.9)	0		0		
T stage						
1	60 (53.6)	21 (72.4)	0.009			
2	27 (24.1)	1 (3.4)				
3	5 (4.5)	4 (13.8)				
4	2 (1.8)	1 (3.4)				
Unknown	18 (16.1)	2 (6.9)				
N stage			0.949			
N0	52 (46.4)	18 (62.1)				
N1	16 (14.3)	5 (17.2)				
N2	17 (15.2)	4 (13.8)				
Unknown	27 (24.1)	2 (6.9)				
M stage			0.206			n/a
M0	112 (100)	28 (96.6)				
M1	0	1 (3.4)				
Resection			<0.001		<0.001	0.001
No resection	0	1 (3.4)		9 (33.3)		
Lobectomy	64 (57.1)	14 (48.3)		4 (14.8)		
Sleeve lobectomy	7 (6.3)	0		0		
Pneumonectomy	9 (8.0)	0		0		
Wedge resection	11 (9.8)	8 (27.6)		13 (48.1)		
Segmental resection	2 (1.8)	5 (17.2)		1 (3.7)		
Bilobectomy	8 (7.1)	1 (3.4)		0		
Endobronchial approach	11 (9.8)	0		0		
Lymph node dissection	57 (50.9)	5 (17.2)	0.001	5 (18.5)	0.002	1.00

bpNET, bronchopulmonary neuroendocrine tumor; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; M, metastasis; n/a, not applicable; N, nodal; T, tumor; WHO PS: WHO performance status.

died because of their bpNET in the sp-bpNET group. Six of them (5.3%) had an unknown cause of death but were considered to have died of bpNET owing to the presence of metastatic disease at last follow-up and occurrence of death less than or equal to 6 months afterward. Taking censoring of patients into account, most patients with sp-bpNET died of bpNET (50% at 10 y of follow-up, 70% at 25 y). In both the MEN1 and DIPNECH group no patients had died of bpNET. Four patients (3.6%) in the sp-bpNET group and four patients (13.8%) in the MEN1 group died of other causes. In the MEN1-group, only one of the patients died of a MEN1-related cancer (thymic NET), all other causes of death were non–MEN1-related cancers or the complications thereof. No deaths occurred in the DIPNECH group. Median disease-specific survival was shorter for patients with sp-bpNET, namely 12.3 years (95% confidence interval: 7.4–17.1), whereas this was not estimable for patients with MEN1 or DIPNECH. The logrank test revealed a significantly different survival distribution between subgroups ($p < 0.001$). Survival curves for all subgroups are shown in Figure 1.

In the sp-bpNET group, patients with AC had a significantly worse survival than patients with TC

Table 2. Pathologic Characteristics for the Three Subgroups, According to TC and AC classification

Characteristics N (%)/Median (Range)	Sporadic bpNET	MEN1	Sporadic vs. MEN1 *p*-Value	DIPNECH	Sporadic vs. DIPNECH *p*-Value	MEN1 vs. DIPNECH *p*-Value
TC	73	20		23		
Ki67-index (%)	3 (0-16)	2 (1-5)	0.948	1 (0-5)	0.077	0.462
Mitotic count/2 mm^2	1 (0-8)	1 (0-2)	0.623	1 (0-1)	0.231	0.253
AC	38	9		4		
Ki67-index (%)	7.5 (0-30)	10 (1-20)	0.704	2.5 (2-3)	0.089	0.250
Mitotic count/2 mm^2	3 (0-27)	4 (2-10)	0.762	2 (2-2)	0.414	0.418
Necrosis[a]			0.029		0.104	0.119
Not present	20 (52.6)	7 (77.8)		1 (25.0)		
Present	15 (39.4)	0		1 (25.0)		
Unknown	3 (7.8)	2 (22.2)		2 (50.0)		

[a]Because the presence of necrosis is a characteristic in the definition the tumor classification for atypical carcinoids, this was only assessed for ACs.
AC, atypical carcinoid; bpNET, bronchopulmonary neuroendocrine tumor; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; TC, typical carcinoid.

($p = 0.003$). Survival curves for TC and AC in sp-bpNET are shown in Figure 2.

Comparison Between Subgroups

sp-bpNET With MEN1. Patients with sp-bpNET were significantly older at time of diagnosis (54 versus 44 y in the MEN1 group, $p = 0.008$). Patients with MEN1 more often had T1 (72.4% versus 53.6%) or T3 tumors (13.8% versus 4.5%). Histologic classification (typical versus atypical) and N-stage was comparable between the two groups. Tumor necrosis occurred more frequently in ACs of patients with sp-bpNET (39.4% versus 0%). No metastatic disease was present in patients with sp-bpNET, compared with one patient (3.4%) with M1 disease in the MEN1 group; this was a histologically confirmed contralateral pulmonary lesion. In patients with sp-bpNET, significantly more anatomical resections (78.6% versus 51.7%, $p = 0.008$) and more lymph node dissections (50.9% versus 14.2%, $p = 0.001$) were performed.

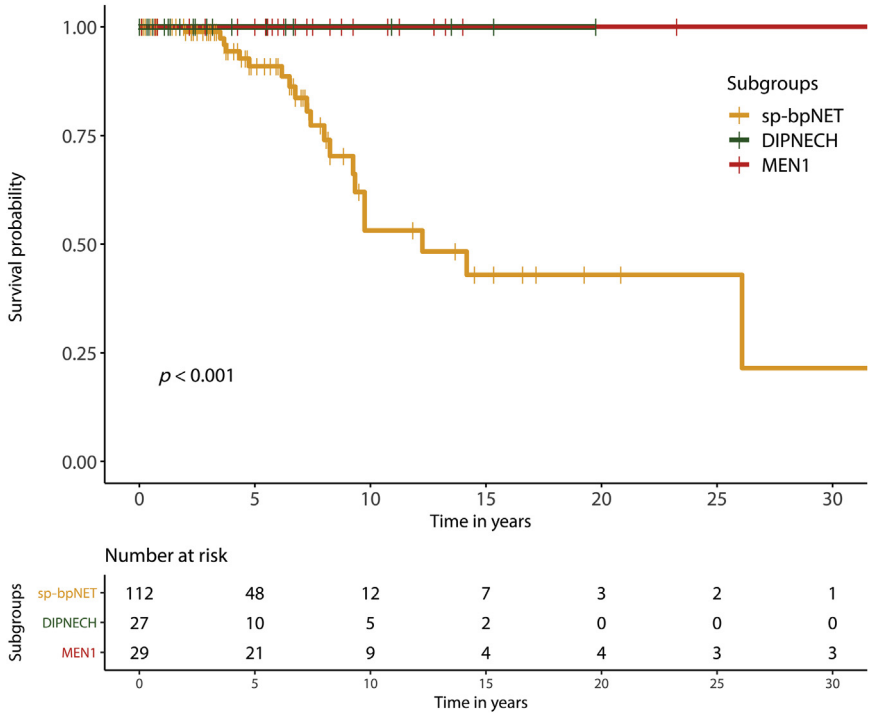

Figure 1. Kaplan-Meier curves for disease-specific survival. *p*-value shows logrank test for comparison between disease-specific survival. sp-bpNET, sporadic bronchopulmonary neuroendocrine tumor; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

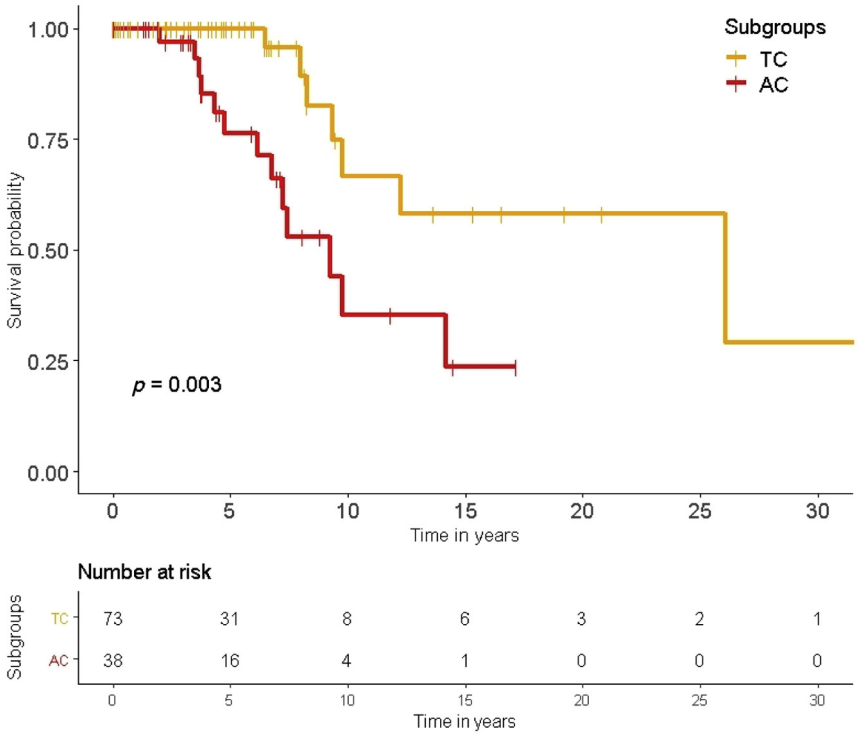

Figure 2. Kaplan-Meier curves for disease-specific survival for sp-bpNET, according to tumor classification. AC, atypical carcinoid; sp-bpNET, sporadic bronchopulmonary neuroendocrine tumor; TC, typical carcinoid.

sp-bpNET With DIPNECH. Patients in the DIPNECH group had a significantly higher age at diagnosis (64 y versus 54 y, $p < 0.004$) and female predominance was more pronounced in this group (100% versus 58.9% females). In addition, similar to MEN1 patients, DIPNECH patients had significantly less anatomical resections (14.8% versus 78.6%, $p < 0.001$) and lymph node dissections (18.5% versus 50.9%, $p = 0.002$), compared with patients with sp-bpNET.

MEN1 With DIPNECH. Patients with MEN1 were younger at time of diagnosis compared with patients with DIPNECH (44 y versus 64 y), and more MEN1 patients were male (34.5% versus 0%). Finally, less patients underwent resection in the DIPNECH group (66.7% versus 96.5%).

Risk Factors for Disease-Specific Mortality in sp-bpNET

Risk factors for DSM in sp-bpNET are illustrated in Table 3. Univariable survival analysis for patients with sp-bpNET identified age at diagnosis (hazard ratio [HR] = 1.09), AC (HR = 4.70), Ki67-index (HR = 1.17), mitotic count (HR = 1.07) and lymph node dissection (HR = 2.52) as risk factors for DSM. Because the number of disease-specific deaths was limited, multivariable cox regression was performed with selected variables that were deemed most contributing to DSM, according to prior clinical knowledge. Hence, age at diagnosis and tumor classification (typical versus atypical) were included in the model. Both variables were identified as independent risk factors for DSM; a HR of 1.09 ($p = 0.001$) was found for age at diagnosis, and HR of 3.61 ($p = 0.009$) for AC. Results of univariable and multivariable analysis can be found in Table 3.

Discussion

Results from this head-to-head comparison study revealed that patients with sp-bpNET had a higher DSM than patients with MEN1-related bpNET, despite similar histologic classification and a more aggressive surgical approach in patients with sp-bpNET. Furthermore, patients with DIPNECH-related and MEN1-related bpNET were found to have a similar outcome. Finally, age at diagnosis and histologic classification revealed to be an independent prognostic factor for survival in sp-bpNET.

The relatively good prognosis of MEN1-related bpNET in this study is in line with earlier findings in other MEN1 cohorts.[9-12] To our knowledge, only eight bpNET-related deaths in patients with MEN1 have been reported to date. In the largest cohort of histologically proven MEN1-related bpNET (n = 51), median overall survival was 20.2 years and not significantly different

Table 3. Univariable and Multivariable Analysis for Disease-Specific Mortality in Sporadic bpNETs

	Univariable			Multivariable		
Characteristics	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age at diagnosis	1.09	1.04-1.14	<0.001	1.09	1.04-1.14	0.001
Sex						
Male	1					
Female	0.52	0.22-1.25	0.143			
WHO PS						
0	1					
1	2.24	0.85-5.90	0.104			
2	1.9	0.18-12.36	0.711			
Tumor classification						
Typical	1			1		
Atypical	4.70	1.81-12.18	0.001	3.61	1.38-9.44	0.014
Ki67-index (%)	1.17	1.10-1.26	<0.001			
Mitotic count/2 mm^2	1.07	1.002-1.13	0.044			
T stage						
1	1					
2	0.89	0.32-2.47	0.692			
3	3.73	0.44-31.83	0.148			
N stage						
0	1					
1	1.94	0.58-6.52	0.283			
2	2.72	0.70-10.51	0.147			
Lymph node dissection	2.52	1.02-6.22	0.045			

bpNET, bronchopulmonary neuroendocrine tumor; CI, confidence interval; HR, hazard ratio; N, nodal; T, tumor; WHO PS, WHO performance status.

from the rest of the cohort (HR: 0.29, [95% confidence interval: 0.02–5.14]).[12] Likewise, the absence of bpNET-related deaths in patients with DIPNECH in our cohort underlines the excellent prognosis of patients with DIPNECH described by others previously.[19-24] Also, the female predominance and high age at diagnosis (median = 63 y) in our cohort of patients with DIPNECH are comparable with other cohorts.[23]

In line with previous research, patients with sporadic atypical lung carcinoid and older patients had significantly worse survival than patients with a TC.[3-6] Others have identified additional prognostic factors associated with adverse prognosis for sp-bpNET, which – among others – were male sex, peripheral tumors and TNM stage.[5,7] Although survival was worse for patients with sp-bpNET as compared with patients with MEN1-related bpNET or DIPNECH, the number of disease-specific events was modest. This prevented us to accurately investigate additional prognostic parameters in our study.

The question arises what could explain the difference in survival between patients with sporadic and MEN1-related bpNET. Although the limited power prevents us to draw firm conclusions, the similarities in tumor classification, Ki67-index and mitotic count between both groups suggest that these histopathological prognostic factors are not responsible for the striking differences in mortality. This is also underscored by the decreasing survival in both TC and AC in sp-bpNET, compared with MEN1-related bpNET. This shows that even the more favorable TCs behave much more aggressively in sp-bpNET, compared with MEN1-related bpNET. Interestingly, several factors could arguably have led to a better survival in patients with sp-bpNET: firstly, patients with sp-bpNET were treated more aggressively, with more anatomical resections and lymph node dissections. Secondly, the lack of lymph node involvement was based on imaging studies in 12 of 18 (67%) MEN1 patients, while N-status in sp-bpNET was based on pathology reports in all cases. This could have resulted in an underestimation of the number of patients with lymph node involvement in the MEN1 group. Patients with sp-bpNET revealed a significantly higher DSM nonetheless, underscoring the different course of disease between these two groups. Thirdly, indication bias could have led to the inclusion of more aggressive MEN1-related lung NET: large tumor size and high growth rate frequently are indications for surgery in MEN1 patients with thoracic nodules suspect of bpNET.[16] Nevertheless, distribution of tumor sizes was quite heterogeneous across the subgroups of MEN1 and sp-bpNET. Although patients with MEN1 had more T1 tumors compared with sp-bpNET patients, they also had a larger proportion of T3 or higher tumors, whereas patients with sp-bpNET had more intermediate (T2) tumors. This can be explained by the often multifocal occurrence of MEN1-related bpNET: the T3 classification

of all MEN1-related tumors were based on the presence of a second tumor in the same lobe, while the only MEN1 patient with T4 suffered from two tumors in the same lobe and tumor spread into a major vein. Obviously, patients with sp-bpNET have to develop tumors large enough to cause symptoms before they are recognized, while MEN1-related bpNET are usually identified as a small asymptomatic nodule during periodic thoracic surveillance. This latter situation might prompt earlier intervention compared with the sp-bpNET group, thereby possibly explaining the difference in prognosis between groups. However, we saw no differences in N-stage between the two subgroups, which implies that the difference in T-stage did not lead to difference in metastatic disease. Taking into account the aforementioned factors, we still saw a lower DSM in patients with MEN1-related bpNET than in their sporadic counterparts, underlining the true different nature of sporadic bpNET when compared with MEN1-related bpNET.

Possibly, unidentified underlying molecular processes are responsible for the difference in outcome. This hypothesis is supported by recent data from Simbolo et al.[29] In their study, next-generation sequencing (NGS) in ACs and LCNECs distinguished three transcriptional clusters; patients with a bpNET in the cluster characterized by frequent somatic *MEN1* mutations had a longer cancer-specific survival compared with a cluster with concurrent inactivation of tumor protein p53 gene and retinoblastoma one gene. However, this seems to contradict previous findings by the same research group: in a subset of 35 atypical lung carcinoids, the presence of a somatic *MEN1* mutation was associated with worse disease-specific survival ($p = 0.0045$).[30] In addition, lung carcinoids and high-grade neuroendocrine carcinomas with inactivation of *MEN1* had shorter survival and low *MEN1* mRNA levels correlated with distant metastasis and shorter survival.[31] Therefore, the precise role of *MEN1* mutations in the natural course and prognosis of bpNET is yet to be determined and requires further research into the molecular background of these tumors.

As for patients with DIPNECH, we revealed that the clinical behavior is highly comparable with that of MEN1-related bpNET. Interestingly, although the proportion of atypical and TCs was similar across all subgroups, there seems to be a trend toward a significantly lower mitotic count and Ki67-index range for patients with DIPNECH compared with the other two subgroups. Especially, there is a notable difference in the ranges of mitotic count and Ki67-index, with a maximum mitotic count of two and a maximum Ki67-index of five for patients with DIPNECH. Arguably, patients who develop DIPNECH-related bpNET might be on an even more favorable end of the lung carcinoid spectrum. This suggests that the subtypes of bpNET in some ways parallel those in gastric NET; type 1 gastric NET is associated with (autoimmune) chronic atrophic gastritis and is characterized by multiple lesions but has an excellent prognosis, illustrated by a very low frequency of submucosal invasion or metastasis (like DIPNECH-related bpNET). Type 2 gastric NETs are usually detected in patients with MEN1-related gastrinomas, invade into the underlying tissue somewhat more often than type 1 gastric NET but still have a very good prognosis with only a small risk of disease-related death (like MEN1-related bpNET). On the contrary, type 3 gastric NETs – which arise sporadically – reveal a more aggressive course with frequent metastasis to lymph nodes (50%–100%) and liver (22%–75%), resulting in a prognosis similar to gastric adenocarcinoma (which seems to mirror characteristics of sp-bpNET).[32]

Some limitations must be considered when interpreting these results. Firstly, the retrospective nature of this study could have influenced the results owing to the dependency on accurate record keeping. However, we did not encounter large issues with missing data. Data concerning WHO performance status (WHO PS) of patients with MEN1-related bpNET could not be retrieved. Although WHO PS might be associated with survival, because this parameter was already quite favorable in patients with sp-bpNET—with most patients having WHO PS 0 to 1—we do not expect that differences might have contributed to a worse survival for patients with sp-bpNET. Furthermore, tumor T- and N-stage at time of diagnosis were unknown in a considerable proportion of patients with sporadic bpNET (16% and 24%, respectively), presumably owing to the aspect of the NKI and UMCU functioning as a tertiary referral center: patients with sp-bpNET were often referred to our center years after initial resection, leading to missing data in some cases. However, we have no reason to believe that the distribution of T- and N- stage of sp-bpNET has been considerably affected by these missing data.

Secondly, pathologic samples of MEN1-related bpNET did not undergo revision. Because DIPNECH is a novel diagnosis, it might be possible that (some) MEN1-related bpNET fall in the DIPNECH category if material were to be revised. Nevertheless, this study is the first step in acknowledgment that MEN1-related bpNET are a truly different entity than sp-bpNET, and future research should be aimed in more in-depth comparison of MEN1-related bpNET and DIPNECH-related bpNET, including revision of available MEN1-related bpNET samples.

Thirdly, despite the relatively large cohort of patients with bpNET, the number of deaths was limited. This prevented us from analyzing survival in bpNET in more detail. Ideally, we would have liked to compare DSM

between groups while adjusting for prognostic factors, like age at diagnosis. However, the lack of bpNET-related death in patients with MEN1- and DIPNECH-related bpNET already underscore the true divergent nature of these entities compared with sp-bpNET. Furthermore, we were able to identify the two most important prognostic factors for DSM in sp-bpNET, that is, age at diagnosis and histologic classification (TC versus AC). A follow-up study with even longer follow-up and more patients might result in sufficient events to analyze prognosis in these subgroups in more detail.

Finally, the predisposition to develop multiple neuroendocrine tumors (NET) in MEN1 patients could have led to a selection of MEN1 patients included in this analysis, thereby affecting comparability between groups: among other manifestations, MEN1 patients are susceptible to the occurrence of duodenopancreatic NET, one of the major causes of MEN1-related death. Events like these earlier in life might have prevented the diagnosis of bpNET in a considerable part of the MEN population, owing to (1) MEN1-related death, or (2) a lack of histologic diagnosis of bpNET owing to refraining from biopsy or lung surgery owing to (presumed) metastatic disease or poor WHO PS. Theoretically, this might have caused us to miss patients that would have developed bpNET later in life, and perhaps would have shown a more aggressive disease course. Nevertheless, our selection of patients—by including only those patients with histologically confirmed bpNET—was done in such a manner to ensure comparability with sp-bpNET. In addition, this selection remains a true representation of clinical practice over a long time period.

To the best of our knowledge, this study is the first to directly compare the outcome of patients with bpNET in the context of MEN1, DIPNECH and the sporadic variant. Despite the rarity of these entities, we were able to include a relatively large cohort by using data from the NKI and UMCU combined ENETS CoE and the population-based Dutch MEN1 Study Group cohort of MEN1 patients. Furthermore, all participating institutions have a team of specialists dedicated to neuroendocrine tumors, including thoracic radiologists and pathologists, which has strengthened the quality of data. Finally, the standardized and comprehensive data collection ensured precise and detailed information about relevant patient and tumor characteristics.

In conclusion, sporadic and MEN1-related bpNET are currently considered the same disease, but results from this study reveal that there is a significant difference in survival between these groups despite similar histopathological features. Paradoxically, several factors (such as the more aggressive surgical approach in sp-bpNET, possible underestimation of proportion of MEN1-related bpNET with lymph node involvement and the probable indication bias leading to a selection of aggressive MEN1-related bpNET) arguably could have led to a better survival in patients with sp-bpNET compared with MEN1-related bpNET, underscoring the true different nature of these two entities. A possible effect of earlier detection of MEN1-related bpNET cannot be excluded entirely, although potential differences in tumor size at time of surgical resection had not resulted in a difference in locoregional or distal spread. The remarkable difference in survival suggests that these are truly distinctive entities. Furthermore, patients with MEN1- and DIPNECH-related bpNET revealed similar survival, suggesting that these entities are more alike, with no bpNET-related death in our study despite the presence of AC in a considerable part of these groups. These findings call for verification in other large cohort studies and further research into underlying explanatory (molecular) mechanisms, potentially leading to prognostic guidelines for different subgroups of bpNET.

CRediT Authorship Contribution Statement

Wieneke A. Buikhuisen, Margot E. T. Tesselaar, Gerlof D. Valk: Conceptualization.

Medard F. M. van den Broek, Sonja Levy, Kim Dijke: Data curation.

Sonja Levy: Formal analysis;

Medard F. M. van den Broek, Sonja Levy, Margot E. T. Tesselaar, Gerlof D. Valk: Investigation, Resources, Software.

Medard F. M. van den Broek, Sonja Levy, Koen J. Hartemink, Rachel S. van Leeuwaarde, Margot E. T. Tesselaar, Gerlof D. Valk: Methodology.

Margot E. T. Tesselaar, Gerlof D. Valk: Supervision.

Medard F. M. van den Broek, Sonja Levy: Visualization, Roles/writing - original draft, Project administration.

Medard F. M. van den Broek, Sonja Levy, Wieneke A. Buikhuisen, Kim Dijke, Koen J. Hartemink, Rachel S. van Leeuwaarde, Menno R. Vriens, Margot E. T. Tesselaar, Gerlof D. Valk: Writing - review and editing.

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