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Neuroendocrine Tumor Heterogeneity Adds Uncertainty to the World Health Organization 2010 Classification: Real-World Data from the Spanish Tumor Registry (R-GETNE)

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a complex family of tumors of widely variable clinical behavior. The World Health Organization (WHO) 2010 classification provided a valuable tool to stratify neuroendocrine neoplasms (NENs) in three prognostic subgroups based on the proliferation index. However, substantial heterogeneity remains within these subgroups, and simplicity sometimes entails an ambiguous and imprecise prognostic stratification. The purpose of our study was to evaluate the prognostic impact of histological differentiation within the WHO 2010 grade (G) 1/G2/G3 categories, and explore additional Ki-67 cutoff values in GEP-NENs.

Subjects, Materials, and Methods. A total of 2,813 patients from the Spanish National Tumor Registry (RGETNE) were analyzed. Cases were classified by histological differentiation as NETs (neuroendocrine tumors [well differentiated]) or NECs (neuroendocrine carcinomas [poorly differentiated]), and by

Ki-67 index as G1 (Ki-67 <2%), G2 (Ki-67 3%–20%), or G3 (Ki-67 >20%). Patients were stratified into five cohorts: NET-G1, NET-G2, NET-G3, NEC-G2, and NEC-G3.

Results. Five-year survival was 72%. Age, gender, tumor site, grade, differentiation, and stage were all independent prognostic factors for survival. Further subdivision of the WHO 2010 grading improved prognostic stratification, both within G2 (5-year survival: 81% [Ki-67 3%–5%], 72% [Ki-67 6%–10%], 52% [Ki-67 11%–20%]) and G3 NENs (5-year survival: 35% [Ki-67 21%–50%], 22% [Ki-67 51%–100%]). Five-year survival was significantly greater for NET-G2 versus NEC-G2 (75.5% vs. 58.2%) and NET-G3 versus NEC-G3 (43.7% vs. 25.4%).

Conclusion. Substantial clinical heterogeneity is observed within G2 and G3 GEP-NENs. The WHO 2010 classification can be improved by including the additive effect of histological differentiation and the proliferation index. *The Oncologist* 2018;23:422–432

Implications for Practice: Gastroenteropancreatic neuroendocrine neoplasms are tumors of widely variable clinical behavior, roughly stratified by the World Health Organization (WHO) 2010 classification into three subgroups based on proliferation index. Real-world data from 2,813 patients of the Spanish Registry RGETNE demonstrated substantial clinical heterogeneity within grade (G) 2 and G3 neuroendocrine neoplasms. Tumor morphology and further subdivision of grading substantially improves prognostic stratification of these patients and may help individualize therapy. This combined, additive effect shall be considered in future classifications of neuroendocrine tumors and incorporated for stratification purposes in clinical trials.

INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a heterogeneous family of tumors of increasing incidence [1]. The wide array of proposed classifications for these tumors over the last decades illustrates their complex biological nature [2–4]. The World Health Organization (WHO) 2000/2004 classification incorporated a number of major predictors of patient outcome, including tumor differentiation and size, lymphovascular invasion, proliferation index, functionality, and extent of distant spread [4]. It also acknowledged the relevance of tumor anatomical location. This classification was an important step forward in the field as it was the first to stratify patients according to prognosis. Some major drawbacks, however, included the confusing mixture of pathological and clinical features (i.e., functionality, staging), as well as the introduction of an ambiguous category of "uncertain behavior."

To overcome some of these caveats, the WHO classification was updated in 2010 [4]. Several changes were introduced in this new classification, such as the terms "neuroendocrine," to reflect some unique features of these tumors (i.e., the expression of neural antigens), and "neoplasm," to encompass the whole family of neuroendocrine cancer. Neuroendocrine neoplasms (NENs) include both the previously designated "carcinoids/well-differentiated endocrine tumors/well-differentiated carcinomas," now termed as neuroendocrine tumors (NETs), and the previously designated "poorly differentiated carcinomas," now termed as neuroendocrine carcinomas (NECs). All NENs are considered potentially malignant, although the prognosis significantly varies among subgroups. Importantly, the classification of NENs as NETs or NECs was established by a proliferation-based grading system that, according to specific Ki-67 index and mitotic count cutoff values, subdivided NETs as grade (G) 1 (Ki-67 index <2% and mitotic count <2/10 high-power fields [HPF]) or G2 (Ki-67 index 3%–20% and/or mitotic count 2–20/10 HPF), and considered all G3 (Ki-67 index >20% and/or mitotic count >20/10 HPF) as NECs, regardless of tumor differentiation.

The WHO 2010 classification has proven to be simple, objective, and reproducible, and has definitively established the proliferation rate as a solid prognostic factor in GEP-NENs [5–7]. However, the cutoff values employed in this classification are somewhat arbitrary, and it is operatively disconnected from important aspects of tumor morphology. Indeed, a number of reports have questioned these cutoff values [8–10] and have also suggested G3 NECs are more heterogeneous than expected [11–15].

In this context, the aim of our study was to evaluate the prognostic impact of histological differentiation within the WHO 2010 G1/G2/G3 categories and explore additional Ki-67 cutoff values in GEP-NENs. For this purpose, real-world data from 2,813 patients registered in the Spanish National Neuroendocrine Tumor Registry (RGETNE) were analyzed. As new classifications are generally gradually implemented in standard practice, whereas old ones take some time to be dismissed, 1,535 registered patients had been classified by both WHO 2000/2004 and WHO 2010 classifications; therefore, information regarding both grade, based on the proliferative index (Ki-67 <3%, 3%–20%, >20%), and histological differentiation (well-differentiated tumors—NETs—or poorly differentiated carcinomas—NECs) was available for these patients.

SUBJECTS, MATERIALS, AND METHODS

Study Population and Design

The study population was obtained from the Spanish National Cancer Registry for GEP-NENs, RGETNE (data cutoff date for analyses: April 2016), a hospital-based tumor registry coordinated by GETNE (Grupo Español de Tumores Neuroendocrinos [its Spanish acronym]), an NEN multidisciplinary scientific society. Data are provided online through a centralized web platform (https://www.e-crd.net/rgetne/) by investigators from 58 academic and community sites representing all regions of Spain (supplemental online Appendix 1). Comprehensive information regarding patient and tumor characteristics, diagnostic and therapeutic interventions, and clinical outcomes are registered from each patient as previously described [9, 16]. To ensure homogeneity in data registration between different notifiers, a technical manual is available online that includes instructions for use and procedures, glossaries with precise definitions of relevant terms and variables, and main tumor classifications. Quality checks are automatically implemented through different software filters, and data are also systematically assessed for internal consistency by external independent reviewers (P.J-F, A.C-B, A.C-P, and R.G-C). In addition, on-site data monitoring/audit has been performed for 51% of registered patients by a medical oncologist with particular expertise in NENs during 2015–2016 (B.N-V). The registry protocol and informed consent (supplemental online Appendices 2, 3) have been approved by a National Scientific and Ethical Committee (translation to English of the registry protocol is provided in supplemental online Appendix 4).

The overall study population included 2,813 patients registered from 2000 through 2016. Of these, 1,535 had been

Table 1. Characteristics of study population

Characteristic	All patients (*n* = 2,813), *n* (%)	pNET (*n* = 975), *n* (%)	giNET (*n* = 1,559), *n* (%)	Other GEP-NETs (*n* = 279), *n* (%)
Age (years)				
Median (range)	58 (10–96)	57 (12–85)	59 (10–96)	63 (14–89)
<30	138 (5.0)	42 (4.3)	92 (5.9)	4 (1.4)
30–60	1,410 (50.2)	544 (55.8)	751 (48.2)	115 (41.2)
>60	1,265 (44.9)	389 (39.9)	716 (45.9)	160 (57.3)
Gender				
Men	1,525 (54.2)	525 (53.8)	849 (54.5)	151 (54.1)
Women	1,288 (45.8)	450 (46.2)	710 (45.5)	128 (45.9)
MEN1 syndrome	90 (3.1)	73 (7.5)	11 (0.7)	6 (2.2)
Genetic test carried out	158 (5.6)	112 (11.5)	37 (2.4)	9 (3.2)
Multiple primary tumors	292 (10.4)	73 (7.5)	216 (13.9)	3 (1.1)
Hormonal syndrome	661 (23.5)	270 (27.7)	330 (21.2)	61 (21.9)
Type of hormonal syndrome				
Carcinoid syndrome	369 (13.1)	16 (1.6)	305 (19.6)	48 (17.2)
Zollinger-Ellison syndrome	69 (2.5)	42 (4.3)	21(1.3)	6 (2.2)
Insulinoma-Hypoglycemia	133 (4.7)	132 (13.5)	—	1 (0.4)
Glucagonoma syndrome	29 (1.0)	27 (2.8)	—	2 (0.7)
Somatostatinoma syndrome	8 (0.3)	6 (0.6)	2 (0.1)	—
Verner-Morrison syndrome (VIPoma)	15 (0.5)	13 (1.3)	—	2 (0.7)
Pancreatic NET with ectopic HP	27 (0.9)	25 (2.6)	1 (0.1)	1 (0.4)
Pancreatic with mixed syndrome	11 (0.4)	9 (0.9)	1 (0.1)	1 (0.4)
NR	46 (1.6)	—	1 (0.1)	45 (16.1)
Reasons for consultation				
Secretory symptoms	426 (15.1)	204 (20.9)	176 (11.3)	46 (16.5)
Incidental diagnosis	954 (33.9)	306 (31.4)	591 (37.9)	57 (20.4)
Non-secretory symptoms	1,064 (37.8)	355 (36.4)	590 (37.8)	119 (42.7)
NR	369 (13.1)	110 (11.3)	202 (13.0)	57 (20.4)
TNM stage at dx				
I	652 (23.2)	212 (21.7)	427 (27.4)	13 (4.7)
II	244 (8.7)	105 (10.8)	132 (8.5)	7 (2.5)
III	366 (13.0)	83 (8.5)	280 (18.0)	3 (1.1)
IV	1,232 (43.8)	448 (45.9)	547 (35.1)	237 (84.9)
NR	319 (11.3)	127 (13.0)	173 (11.1)	19 (6.8)
Localization of metastases at dx				
Liver	1,101 (39.1)	438 (44.9)	480 (30.8)	183 (65.6)
Lymph nodes	360 (12.8)	130 (13.3)	143 (9.2)	87 (31.2)
Peritoneum	221 (7.9)	39 (4.0)	147 (9.4)	35 (12.5)
Bone	146 (5.2)	42 (4.3)	44 (2.8)	60 (21.5)
Lung	99 (3.5)	25 (2.6)	39 (2.5)	35 (12.5)
Ki-67 (%)				
<2	689 (24.5)	199 (20.4)	467 (30.0)	23 (8.2)
3–5	347 (12.3)	138 (14.2)	180 (11.5)	29 (10.4)
5–10	190 (6.8)	108 (11.1)	63 (4.0)	19 (6.8)
11–20	143 (5.1)	90 (9.2)	34 (2.2)	19 (6.8)
21–50	132 (4.7)	51 (5.2)	51 (3.3)	30 (10.8)
>50	178 (6.3)	29 (3.0)	108 (6.9)	41 (14.7)
NR	1,134 (40.3)	360 (36.9)	656 (42.1)	118 (42.3)

(continued)

Table 1. (continued)

Characteristic	All patients (*n* = 2,813), *n* (%)	pNET (*n* = 975), *n* (%)	giNET (*n* = 1,559), *n* (%)	Other GEP-NETs (*n* = 279), *n* (%)
WHO 2010				
G1	697 (24.8)	200 (20.5)	474 (30.4)	23 (8.2)
G2	738 (26.2)	357 (36.6)	310 (19.9)	71 (25.4)
G3	364 (12.9)	91 (9.3)	188 (12.1)	85 (30.5)
NR	1,014 (36.0)	327 (33.5)	587 (37.7)	100 (35.8)
Histological differentiation				
Well differentiated	1,772 (63.0)	628 (64.4)	1,044 (67.0)	100 (35.8)
Poorly differentiated	335 (11.9)	96 (9.8)	169 (10.8)	70 (25.1)
NR	706 (25.0)	251 (25.7)	346 (22.2)	109 (39.1)

Percentages represent proportions of the columns.

p values were calculated from Pearson chi-square tests, except for the continuous variable "age," for which the independent samples Kruskal-Wallis test was used.

Abbreviations: —, 0 (0.0); dx, diagnosis; G, grade; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; giNET, gastrointestinal neuroendocrine tumor; HP, hormone production; MEN1, multiple endocrine neoplasia 1; NET, neuroendocrine tumor; NR, not reported; pNET, pancreatic neuroendocrine tumor; TNM, tumor-node-metastases staging system; VIP, vasoactive intestinal peptide; VIPoma, VIP-producing tumor; WHO, World Health Organization.

classified both by the WHO 2000/2004 and WHO 2010 classifications; therefore, information regarding both grade, based on the proliferative index (Ki-67 <3%, 3%–20%, >20%), and histological differentiation (well-differentiated tumors—NETs—or poorly differentiated carcinomas—NECs) was available for these patients (supplemental online Figs. 1, 2). According to both parameters, patients were stratified into five cohorts: NET-G1 (*n* = 609), NET-G2 (*n* = 558), NET-G3 (*n* = 25), NEC-G2 (*n* = 18), and NEC-G3 (*n* = 245).

Study Aims

The main objective was to assess the prognosis of patients with GEP-NENs according to histological differentiation and proliferative index, and to evaluate, with real-world data, the interaction between the WHO 2000 and 2010 classifications to explore the potential independent prognostic value of tumor differentiation within the WHO 2010 G2/G3 categories. The primary endpoint was the 5-year survival rate. Secondary objectives were (a) to explore the effect of additional Ki-67 cutoff values in the prognosis stratification of GEP-NENs patients and (b) to assess other prognostic factors for survival.

Statistical Analysis

Descriptive statistics were used to characterize clinical and pathological parameters. The association of categorical variables was assessed by Pearson chi-square tests. The Kruskal-Wallis test was used for continuous variables. Survival was estimated by the Kaplan-Meier product limit method, and differences observed among subgroups were assessed with the Generalized Wilcoxon test. Variables predictive of survival (*p* < .1) in univariable analyses were entered into the Cox proportional hazards (PH) regression model. Additional variables such as octreotide scan, mitotic count, and chromogranin, 5-hydroxyindolacetic acid, insulin, and serotonin levels were also included in the multiple imputation model. The PH assumption was determined using Schoenfeld residuals. Multiple imputation using fully conditional specification was used in multivariate analysis to deal with missing values [17], as it can provide valid inferences assuming that missing is approximately at

random. Our imputation model focused on Ki-67 percentage and histological grade and stage and took into account multiple variables associated with the imputed data as previously mentioned. The process is iterated 10 times, resulting in 10 imputed datasets that provided the pooled estimates in the Cox PH regression. Complete case analysis was applied to analyze secondary outcomes. Harrell's bias-corrected c-index was used to evaluate discrimination. All statistical assessments were two-sided and *p* values < .05 were deemed statistically significant. Statistical analyses were performed using IBM SPSS version 22.0 (IBM, Armonk, NY) and R software, version 3.3.1 (http://www.r-project.org).

RESULTS

Patient Population

Clinical and pathologic characteristics of the study population (*n* = 2,813 patients) are summarized in Table 1. The most common primary tumor sites included 975 pancreas (34.6%), 518 jejunum-ileum (18.4%), 298 stomach (10.5%), 277 appendix (9.8%), 169 rectum (6.0%), 153 colon (5.4%), and 104 duodenum (3.6%).

Given its gradual introduction into clinical practice, the WHO 2010 classification was registered in 1,799 patients (63% of the overall population), including 697 G1 (39% of classified patients), 738 G2 (41%), and 364 G3 cases (20%). Histological differentiation as per the WHO 2000/2004 classification was documented in 2,107 patients (74% of the overall population), including 1,772 well-differentiated tumors (84% of characterized tumors) and 335 poorly differentiated carcinomas (16%).

A significant proportion of patients had stage IV disease at diagnosis (*n* = 1,232, 43%), although this proportion significantly varied depending on grade and primary tumor site. Stage IV disease was documented at diagnosis in 29%, 53%, and 68% of G1, G2, and G3 NENs, respectively. The primary tumor sites that most frequently presented with stage IV disease were jejunum-ileum (59%), esophagus (50%), colon (49%), and pancreas (46%), whereas it was exceptional in appendix primaries (3%).

Table 2. Prognostic factors for overall survival (univariable analysis)

Characteristic	Patients/events (n)	Median	HR (95% CI)	% at 5 years (95% CI)	p value
All patients	2,813/757	13.1	—	71.9 (69.9–73.8)	—
Gender					<.0001
Men	1,525/452	11.0	Ref.	66.3 (66.3–71.8)	
Women	1,288/305	15.8	0.75 (0.84–0.86)	75.3 (72.3–78.2)	
Age (years)					<.0001
<30	138/13	NC	Ref.	91.1 (85.4–96.7)	
30–60	1,400/312	17.2	2.77 (1.59–4.83)	77.8 (75.2–80.3)	
>60	1,265/421	8.1	5.85 (3.37–10.17)	62.5 (59.1–65.8)	
MEN syndrome					<.0001
No	2,723/746	12.4	Ref.	71.2 (69.0–73.3)	
Yes	90/11	NC	0.31 (1.17–0.56)	90.9 (84.4–97.3)	
Hormonal syndrome					.002
No	2,152/590	11.8	Ref.	70.3 (67.9–72.6)	
Yes	661/167	16.0	0.75 (0.63–0.90)	77.3 (73.3–81.2)	
Type of hormonal syndrome					<.0001
Nonfunctional	2,106/570	12.4	Ref.	70.8 (68.4–73.1)	
Carcinoid syndrome	369/101	11.7	0.96 (0.77–1.18)	73.9 (68.2–79.5)	
Zollinger-Ellison syndrome	69/14	16.4	0.51 (0.30–0.87)	86.6 (77.1–96.0)	
Insulinoma-Hypoglycemia	133/16	NC	0.31 (0.18–0.51)	87.9 (81.4–94.3)	
Glucagonoma syndrome	29/7	NC	0.54 (0.25–1.15)	84.2 (69.8–98.5)	
Somatostatinoma syndrome	8/5	10.8	1.46 (0.60–3.52)	68.6 (32.1–99.9)	
Verner-Morrison syndrome (VIPoma)	15/5	7.5	0.90 (0.37–2.19)	74.1 (48.8–99.3)	
Pancreatic NET with ectopic HP	27/15	5.6	1.99 (1.19–3.32)	53.1 (32.1–74.0)	
Pancreatic with mixed syndrome	11/4	2.6	1.12 (0.46–3.29)	46.3 (9.0–83.5)	
NR	46/20	2.9	2.97 (1.90–4.66)	41.5 (21.4–60.6)	
Primary tumor site					<.0001
Pancreas	975/271	12.0	Ref.	70.2 (66.6–73.7)	
Esophagus	14/9	0.9	6.02 (3.09–11.74)	29.2 (3.32–55.0)	
Stomach	298/78	14.3	1.11 (0.86–1.43)	70.8 (64.5–77.0)	
Duodenum	104/20	15.8	0.64 (0.41–1.02)	86.6 (79.1–94.0)	
Jejunum-ileum	518/109	12.9	0.71 (0.56–0.88)	83.4 (79.4–87.3)	
Appendix	277/27	NC	0.32 (0.21–0.47)	90.5 (85.9–95.0)	
Colon	153/57	11.9	1.58 (1.19–2.11)	60.5 (51.4–69.5)	
Rectum	173/51	10.8	1.26 (0.93–1.70)	63.0 (53.9–72.0)	
Enteric NOS	22/7	2.0	2.91 (1.37–6.19)	50.0 (16.8–83.1)	
Hepatobiliary	34/15	5.5	2.19 (1.30–3.68)	53.6 (34.7–72.4)	
Tumor of unknown primary origin	245/113	4.3	2.29 (1.84–2.86)	47.3 (39.5–55.2)	
TNM stage					<.0001
I	652/55	NC	Ref.	92.6 (90.0–95.1)	
II	244/39	NC	1.05 (1.36–3.09)	82.2 (76.3–88.0)	
III	366/83	15.8	2.85 (1.02–4.01)	81.0 (76.2–85.7)	
IV	1,232/537	5.7	6.96 (5.27–9.19)	52.2 (48.8–55.5)	
NR	319/43	NC	1.16 (1.13–2.53)	88.2 (83.6–92.7)	
Localization of metastases at dx					
Liver	1,101/481	5.8	3.23 (2.78–3.74)	53.3 (49.7–56.8)	<.0001
Lymph nodes	360/165	4.1	2.67 (2.24–3.18)	44.5 (37.5–50.4)	<.0001
Peritoneum	221/96	5.5	2.12 (1.71–2.63)	52.6 (44.5–60.6)	<.0001

(continued)

Table 2. (continued)

Characteristic	Patients/events (n)	Overall survival (years)				
		Median	HR (95% CI)	% at 5 years (95% CI)	p value
Bone	146/72	3.9	2.60 (2.03–3.31)	41.4 (31.0–51.7)	<.0001
Lung	99/62	2.4	4.20 (3.32–5.45)	27.0 (15.8–38.1)	<.0001
Ki-67 (%)					<.0001
<2	689/82	15.8	Ref.	86.4 (82.8–89.9)	
3–5	347/65	12.4	1.47 (1.07–2.05)	80.7 (75.2–86.1)	
6–10	190/43	NC	1.86 (1.29–2.70)	72.0 (63.7–80.2)	
11–20	143/50	6.8	3.53 (2.48–5.02)	52.2 (41.0–63.3)	
21–50	132/75	1.9	8.04 (5.87–11.02)	35.3 (25.3–45.2)	
>50	178/113	0.9	13.27 (9.94–17.71)	21.9 (14.2–29.5)	
NR	1,134/329	15.0	1.86 (1.45–2.37)	74.3 (71.3–77.2)	
WHO 2010					<.0001
G1	697/88	15.8	Ref.	85.8 (82.2–89.3)	
G2	738/169	11.7	1.87 (1.45–2.43)	73.1 (69.3–77.6)	
G3	364/215	1.2	9.27 (7.22–11.91)	28.2 (22.3–34.0)	
NR	1,014/285	16.0	1.73 (1.36–2.09)	75.7 (72.7–78.6)	
Histological classification					<.0001
Well differentiated	1,772/349	16.9	Ref.	80.1 (77.7–82.4)	
Poorly differentiated	335/212	1.2	6.63 (5.57–7.89)	27.5 (21.6–33.3)	
NR	706/196	12.0	1.54 (1.29–1.83)	72.7 (68.5–76.8)	

Test used: Generalized Wilcoxon text (univariable analysis); HRs derive from univariable Cox PH regression.
Based on original data without imputation.
Abbreviations: —, no data; CI, confidence interval; dx, diagnosis; G, grade; HP, hormone production; HR, hazard ratio; MEN, multiple endocrine neoplasia; NC, not computable (reference category or median not reached); NET, neuroendocrine tumor; NOS, not otherwise specified; NR, not reported; PH, proportional hazards; Ref., reference value; TNM, tumor-node-metastases staging system; VIP, vasoactive intestinal peptide; VIPoma, VIP-producing tumor; WHO, World Health Organization.

Overall Survival and Prognostic Factors

At last follow-up, 757 patients (27%) had died. With a mean follow-up of 4.5 years (range: 0–29), the 5-year overall survival (OS) rate for the whole study population was 72% (95% confidence interval [CI]: 69.9–73.8). Survival was significantly greater in women, young people, multiple endocrine neoplasia (MEN) syndrome, and functional tumors (Table 2). Survival rates also significantly differed by tumor grade, histological differentiation, and TNM stage. Of note, prognosis was influenced to a greater extent by tumor grade (5-year OS rates for G1, G2, and G3: 86%, 73%, and 28%, respectively) or tumor differentiation (5-year OS rates for well- vs. poorly differentiated neoplasms: 80% vs. 28%) than by tumor stage (5-year OS rates for stage I, II, III and IV: 93%, 82%, 81%, and 52%; Table 2). All these results were based on original data without imputation.

Primary tumor site was another major determinant of patient outcome. Prognosis was good for NENs of the appendix, jejunum-ileum, or duodenum (5-year OS: 83%–91%), intermediate for gastric or pancreatic NENs (5-year OS: 70%–71%), and poor for colon, rectum, hepatobiliary, or esophageal NENs and for those of unknown primary (5-year OS: 29%–63%). However, these figures are substantially influenced by grade and stage, which are not evenly distributed among different primary tumor sites (Table 3). Based on 10 imputed datasets, the Cox PH regression confirmed age, gender, MEN syndrome, primary tumor site, proliferation-based grade

(WHO 2010), tumor differentiation, TNM stage, and lung metastases as independent prognostic factors for survival (Table 4). The prediction for 5-year OS is well calibrated (Groennesby-Borgan score test: chi-square = 5.924, p = .7475), and a bias-corrected Harrell's c-index of 0.803 (95% CI: 0.782–0.818) was observed.

Relevance of Histological Differentiation and Proliferative Index Subgrading in Prognosis Stratification

To analyze heterogeneity of G2 and G3 NENs according to WHO 2010 classification, we explored further subdivisions of these categories by Ki-67 index (Table 1). This analysis showed a wide spectrum of clinical behavior both for G2 (5-year OS: 81% [Ki-67 3%–5%], 72% [Ki-67 6%–10%], 52% [Ki-67 11%–20%]) and G3 NENs (5-year OS: 35% [Ki-67 21%–50%], 22% [Ki-67 51%–100%]; Fig. 1). To confirm the results of the Cox multivariate analysis and to assess the influence on survival of histological differentiation within the proliferation-based grading system, we performed a sensitivity analysis only with complete cases (patients classified simultaneously with the WHO classification 2000/2004 and 2010; Table 5; Fig. 1). Of 632 G2 NENs with information on tumor differentiation, we identified 611 (96%) well-differentiated tumors (here termed as G2 NET) and 21 (4%) poorly differentiated carcinomas (here termed as G2 NEC) that had significantly different prognosis (OS percentage at 5 years for G2 NET vs. G2 NEC: 75% vs. 58%, p = .001).

Table 3. Overall survival of patients with neuroendocrine neoplasms by primary tumor site, stage, and grade

| Primary tumor location | All stages (I–IV) | | | | | | Stage IV patients | | | | | |
| | All patients | | G1–G2 | | G3 | | All patients | | G1–G2 | | G3 | |
	n	OS, % (5y)	n	OS, % (5y)	n	OS, % (5y)	n	OS, % (5y)	n	OS, % (5y)	n	OS, % (5y)
Pancreas	975	70.2	557	75.3	91	24.6	458	50.4	239	54.7	66	23.2
Esophagus	14	29.2	1	—	10	25.4	7	28.6	1	—	3	0
Stomach	298	70.8	148	81.5	47	17.9	60	11.0	18	32.8	32	0
Duodenum	104	86.6	57	89.8	4	—	20	69.4	10	85.7	2	—
Jejunum-ileum	518	83.4	330	85.6	8	0	306	78.1	202	82.0	8	0
Appendix	277	90.5	116	92.6	12	—	9	61.0	6	37.5	0	—
Colon	153	60.5	44	84.9	63	40.2	73	40.8	21	69.5	35	18.6
Rectum	173	63.0	79	80.0	37	23.6	56	13.3	16	0	23	0
Enteric NOS	22	50.0	8	—	7	—	18	43.2	6	—	7	—
Hepatobiliary	34	53.6	9	87.7	20	19.2	17	29.2	2	—	13	15.3
UK	245	47.3	85	51.1	65	29.1	222	43.0	79	49.6	69	28.1

Cases with unreported grade were not included in this table.
Based on original data without imputation.
Abbreviations: —, no data; 5y, 5 years; G1–G2, grade 1–2 (Ki-67 index ≤20%); G3, grade 3 (Ki-67 index >20%); NOS, not otherwise specified; OS, overall survival; UK, tumor of unknown primary origin.

Table 4. Cox proportional hazards regression model for overall survival

Variable	Estimate	Hazard ratio	95% CI	p value
Age (years)	0.0265	1.0268	1.0201–1.0335	<.0001
Gender (female vs. male)	−0.0776	0.9254	0.7849–1.0909	.3556
MEN syndrome (yes vs. not)	−0.7364	0.4788	0.2435–0.9418	.0329
Hormonal syndrome (yes vs. not)	−0.1639	0.8488	0.6851–1.0517	.1339
Primary tumor site				<.0001
Favorable strata	—	Ref.	Ref.	—
Intermediate strata	0.6474	1.9106	1.5012–2.4317	<.0001
Unfavorable strata	0.6723	1.9587	1.5141–2.5337	<.0001
WHO 2010				<.0001
G1	—	Ref.	Ref.	—
G2	0.1881	1.2070	0.9589–1.5193	.1090
G3	0.8472	2.3331	1.6679–3.2637	<.0001
Histological differentiation (PD vs. WD)	0.7011	2.0159	1.4791–2.7475	<.0001
TNM stage IV	1.1041	3.0166	2.4870–3.6589	<.0001
Bone metastases	0.1013	1.1066	0.8317–1.4723	.4870
Lung metastases	0.7079	2.0297	1.5171–2.7153	<.0001
Peritoneal metastases	0.3458	1.4132	1.1020–1.8122	.0064

Primary tumor site strata: Favorable = appendix, jejunum-ileum, and duodenum; Intermediate = pancreas and stomach; Unfavorable = colon, rectum, unknown, enteric NOS, hepatobiliary, and esophagus.
Cox regression was stratified by the year of diagnosis.
Test of proportional hazards assumption: chi-square = 14.70, p = .401.
Based on imputed data.
Ki-67 percentage not included due to collinearity with the proliferation-based WHO 2010 grade.
Abbreviations: —, no data; CI, confidence interval; G, grade; MEN, multiple endocrine neoplasia; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PD, poorly differentiated; Ref., reference value; TNM, tumor-node-metastases staging system; WD, well differentiated; WHO, World Health Organization.

Similarly, of 288 G3 NENs with information on tumor differentiation, those with well-differentiated tumors or G3 NETs (n = 27, 9%) had a significantly better prognosis than those with poorly differentiated carcinomas or G3 NECs (n = 261, 91%; 5-year OS: 43% vs. 25%, respectively, p = .048). In addition, a sensitivity analysis showed that the effect of histologic differentiation is consistent for both pancreatic and nonpancreatic tumors (data not shown). Main clinical and pathological characteristics of G2 NET/NEC and G3 NET/NEC patients are summarized in Table 5.
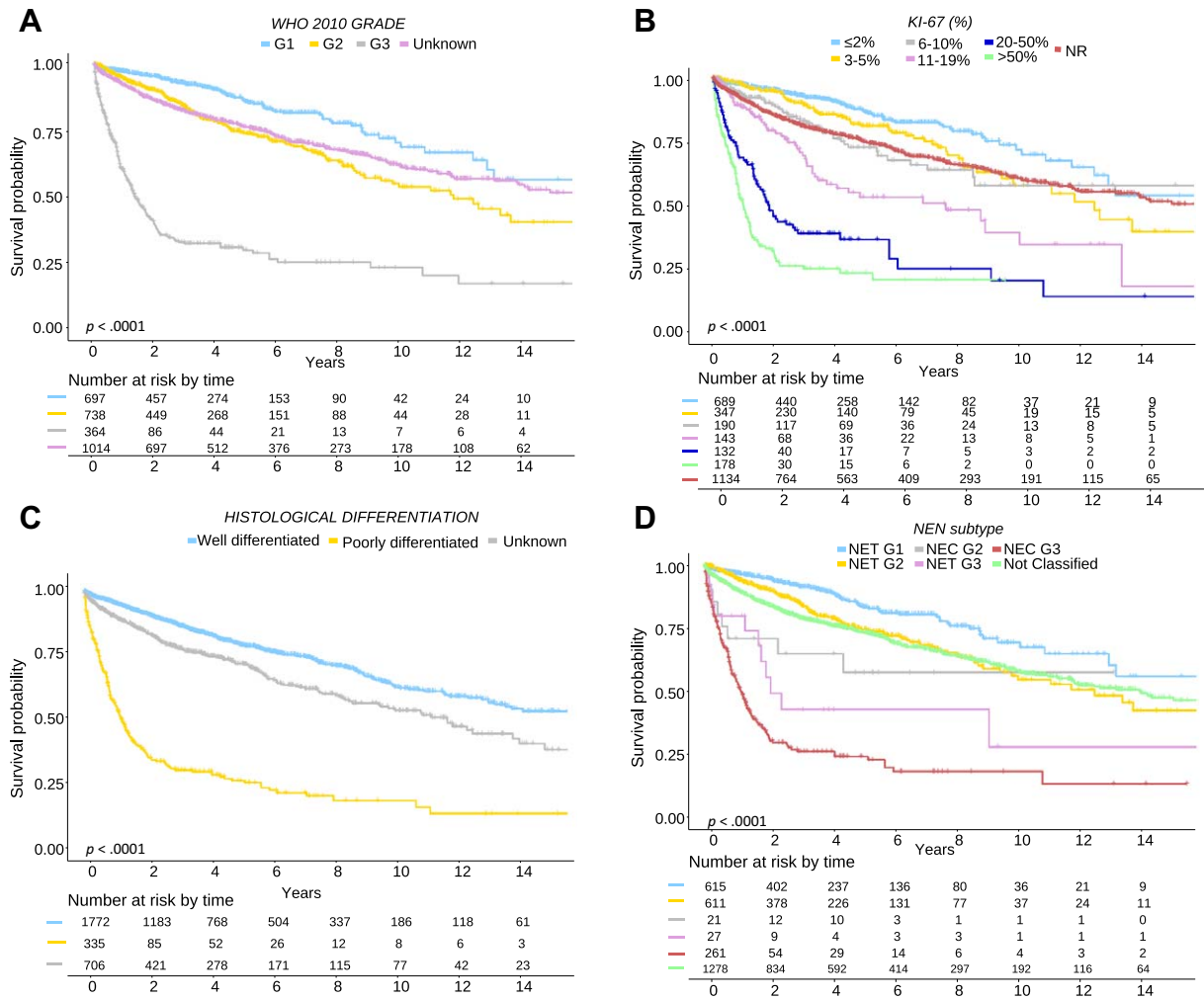
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Figure 1. Overall survival of patients with gastroenteropancreatic neuroendocrine neoplasms by tumor differentiation and proliferation rate. **(A)**: Survival of patients by tumor grade: grade 1 (G1) or Ki-67 ≤2%, grade 2 (G2) or Ki-67 3%–20%, grade 3 (G3) or Ki-67 >20%, unknown (UK) grade or Ki-67 not done or not reported. **(B)**: Survival of patients by Ki-67 proliferation rate: 0%–2%, 3%–5%, 6%–10% 11%–20%, 21%–50%, >50%. **(C)**: Survival of patients by tumor differentiation: well differentiated (NET), poorly differentiated (NEC), unknown tumor differentiation. **(D)**: Survival of patients by tumor grade and differentiation: G1 NET, G2 NET, G2 NEC, G3 NET, G3 NEC. Abbreviations: G, grade; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NR, not reported; WHO, World Health Organization.

DISCUSSION

GEP-NENs are a complex family of neoplasms of widely variable biological behavior [18]. Multiple factors influence outcome, many of which (e.g., proliferation rate, histological differentiation, or tumor site) are more determinant of patient survival than tumor stage [8, 9, 19]. The WHO 2000/2004 classification incorporated to a certain extent all these items. However, the high degree of ambiguity inherent to some of the proposed categories and the somewhat confusing combination of clinical and pathological features limited its widespread use. In this context, the WHO 2010 classification provided a valuable tool to stratify NEN prognosis based on an objective measure, the proliferation index, and has proven to be simple to use and reproducible. Of note, in this classification, quantitative variables (Ki-67 index) have somewhat overridden some important classical histological features. In addition, although tumor categories are easily discernable, emerging data suggest substantial heterogeneity within categories that deserve to be further addressed.

With this purpose, in the present study, we evaluated the prognostic impact of histological differentiation within the WHO 2010 G1/G2/G3 categories, and of additional Ki-67 cutoff values in 2,813 patients with GEP-NENs registered in RGETNE. In our experience, further subdivision of grading improves prognostic stratification of patients, both within G2 (OS percentage at 5 years: 81% [Ki-67 3%–5%], 72% [Ki-67 6%–10%], 52% [Ki-67 11%–20%]) and G3 NENs (OS percentage at 5 years: 35% [Ki-67 21%–50%], 22% [Ki-67 51%–100%]). Particularly remarkable is the impact in prognosis of a Ki-67 cutoff value of 10% for G2 NENs, which identifies a subgroup with significantly worse prognosis within this category (52% 5-year OS for patients with Ki-67 index above this value), although these figures indicate proliferation rate likely behaves as a continuous variable. It should also be highlighted that prognosis of patients with G1 NETs was very similar to the subgroup of G2 NET patients with Ki-67 <5%. Our data also suggest histological differentiation provides useful, additive, and independent prognostic information beyond the proliferation index in patients with GEP-NENs. Indeed, the subgroup of patients with well-

Table 5. Characteristics of patients with G2 and G3 neuroendocrine neoplasms according to tumor differentiation (NET vs. NEC; all stages)

Characteristic	G1 NET, n (%) n = 615	G2 NET, n (%) n = 611	G2 NEC, n (%) n = 21	p value (NET vs. NEC G2)	G3 NET, n (%) n = 27	G3 NEC, n (%) n = 261	p value (NET vs. NEC G3)
Median age (range)	59 (13–96)	58 (10–88)	56 (39–82)	.323	67.0 (33–85)	64.0 (27–89)	.803
Primary tumor location				.744			.403
Unknown	17 (2.8)	47 (7.7)	2 (9.5)		5 (18.5)	45 (17.2)	
Pancreas	169 (27.5)	286 (46.8)	12 (57.1)		11 (40.7)	64 (24.5)	
Stomach	81 (13.2)	54 (8.8)	2 (9.5)		5 (18.5)	32 (12.3)	
Appendix	91 (14.8)	14 (2.3)	0		0	6 (2.3)	
Rectum	46 (7.5)	20 (3.3)	2 (9.5)		0	27 (10.3)	
Duodenum	40 (6.5)	13 (2.1)	0		1 (3.7)	2 (0.8)	
Jejunum-ileum	145 (23.6)	148 (24.2)	2 (9.5)		1 (3.7)	5 (1.9)	
Colon	18 (2.9)	21 (3.4)	1 (4.8)		3 (11.1)	46 (17.6)	
Enteric NOS	4 (0.7)	4 (0.7)	0		0	7 (2.7)	
Esophagus	0	0	0		0	8 (3.1)	
Hepatobiliary	4 (0.7)	4 (0.7)	0		1 (3.7)	19 (7.3)	
Elevated biomarker[a]							
CgA	160 (55.2)	251 (69.1)	7 (87.5)	.265	10 (83.3)	75 (77.0)	.869
NSE	14 (31.1)	28 (53.8)	1 (50)	.948	3 (100.0)	30 (81.1)	.968
Functioning tumors	101 (16.4)	114 (18.7)	1 (4.8)	.265	5 (18.5)	13 (5.0)	.005
Octreoscan positive[a]	226 (69.5)	350 (83.1)	10 (66.7)	.371	9 (63.3)	54 (49.5)	.133
Stage at diagnosis				.241			.273
I–II	369 (60.0)	201 (32.9)	4 (19.0)		1 (3.7)	32 (12.3)	
III	66 (10.7)	78 (12.8)	3 (14.3)		4 (14.8)	48 (18.4)	
IV	176 (28.6)	325 (53.2)	13 (61.9)		20 (74.1)	178 (68.2)	
NR	4 (0.7)	7 (1.1)	1 (4.8)		2 (7.4)	3 (1.1)	
Median survival (months)	278.8	149.9	NR		25.3	14.4	
5-year survival rate, % (95% CI)	84.1 (79.9–88.2)	75.5 (70.9–80.0)	58.2 (35.2–81.1)	.045/.001	43.7 (20.1–66.6)	25.4 (18.9–31.8)	.047/.048

Percentages represent proportions of the columns.
Tests used: Pearson's chi-square test with Yates continuity correction when needed, for categorical variables; the independent samples median test for the continuous variable "age"; log-rank and Wilcoxon test for survival data.
Based on original data without imputation (complete case analysis).
[a]With respect to tested subjects.
Abbreviations: CgA, chromogranin A; CI, confidence interval; G1, grade 1 (Ki-67 index ≤2%); G2 (Ki-67 index 3%–20%); G3, grade 3 (Ki-67 index >20%); NEC, poorly differentiated neuroendocrine carcinoma; NET, well-differentiated neuroendocrine tumor; NOS, not otherwise specified; NR, not reported; NSE, neuronal specific enolase.

differentiated G3 NENs (9% of all G3), the so-called G3 NETs, had a significantly better prognosis than patients with poorly differentiated G3 NENs (G3 NECs; 5-year OS: 42% vs. 24%, respectively, $p = .025$). This effect was consistent for both pancreatic and nonpancreatic tumors. Therefore, our findings are in agreement with the new WHO 2017 classification for endocrine tumors, which was published during the review of this article and includes pancreatic (but not gastrointestinal [GI]) NENs and incorporates for the first time a discrimination of G3 NET from G3 NEC [20]. Our data also suggest that this discrimination may also need to be considered for nonpancreatic NENs. Finally, we also identified a small subgroup of G2 NEN with poorly differentiated histology (3% of all G2, here termed as G2 NEC) that had a significantly worse prognosis than well-differentiated G2 NETs (5-year OS: 57% vs. 75%, respectively, $p = .001$). This is to our knowledge the largest experience reported to date analyzing the interaction of proliferation rate and tumor differentiation and the first one to report on tumor heterogeneity within the G2 NEN category.

Overall prognosis was favorable, with a 5-year OS rate of 72%. Of note, outcome was influenced to a greater extent by tumor grade (5-year OS rates for G1, G2, and G3: 86%, 73%, and 28%, respectively) or tumor differentiation (5-year OS rates for well- vs. poorly differentiated neoplasms: 80% vs. 28%) than by tumor stage (5-year OS rates for stage I, II, III, and IV: 93%, 82%, 81%, and 52%). Primary tumor site was another major independent determinant of patient prognosis, although survival by anatomical localization of the primary tumor observed in our series significantly differed from that reported in the Surveillance, Epidemiology, and End Results (SEER) tumor registry for the U.S. population [1, 21]. Results from RGETNE identified the appendix, jejunum-ileum, or duodenum as the sites with the best prognosis, whereas colon, rectum, hepatobiliary, or esophageal NENs were associated with the poorest prognosis. On the contrary, rectal primaries had an excellent prognosis in the SEER registry, whereas the worst survival figures were reported for pancreatic primaries. It is remarkable that prognosis of patients with pancreatic NENs was substantially better for patients registered in RGETNE than for those of the SEER registry (5-year OS rates of 70% vs. 30%, respectively). A number of potential factors may account for the observed differences, including confounding variables such as grade or stage (the SEER registry does not include "benign" pancreatic NETs), registration biases inherent to hospital-based versus population registries (early-stage gastric or rectal primaries likely underrepresented in RGETNE due to the low participation of gastroenterologists), geographic disparities in terms of racial composition (population in Spain being dominantly white), and other genetic and environmental factors, as well as health care standards and availability (access to care is universally guaranteed in the Spanish Public Health Care System).

These data, however, should be interpreted with caution, as the proportion of patients with poorly differentiated G2 NEN or well-differentiated G3 NEN is low, the follow-up of our series (4.5 years) was somewhat limited for the more indolent subgroups, and information of tumor differentiation and proliferation rate was only available for 55% ($n = 1,535$) of registered patients (grade and histological differentiation were not reported for 37% and 26% of patients, respectively). Nevertheless, results of our study are relevant, as they point out the fact that in current standard practice there are a proportion of patients whose prognostic classification is ambiguous or imprecise and illustrate with real-world data that the prognostic stratification ability of the current WHO 2010 classification may be improved by incorporating histological differentiation and further subdivision of grading.

Other potential limitations of our study include heterogeneity of standards of care and data quality among different institutions, which is a recurring problem in many cancer registries, and the lack of centralized pathological review of critical variables such as tumor differentiation or proliferation rate. In particular, readers should be aware that morphological diagnosis of high-grade NENs may be quite challenging even for experienced pathologists due to the lack of precisely defined criteria, particularly with limited or suboptimal samples [22]. Nevertheless, it was not the aim of this study to test currently available classifications in ideal conditions (i.e., tumors assessed in a uniform way by expert NEN pathologists), but rather to analyze how they perform in the real world. In addition, the availability of a technical manual to ensure homogeneity in data registration between different notifiers, the implementation of automatic and external quality checks, the on-site data monitoring of about half the registered patients by a medical oncologist with particular expertise in NENs, and the rigorous statistical analysis performed have tried to minimize some of these caveats. Another relevant consideration is that our analysis does not differentiate between small- and large-cell variants. This would be an interesting issue to explore, as the large-cell subtype seems to have somewhat better prognosis than small-cell NECs, particularly in the GI tract [23], and it is unclear whether it could also influence response to therapy. However, molecular profiling suggests both subtypes harbor common genetic alterations that differ from those encountered in well-differentiated NETs [24], and current guidelines indicate similar clinical management for both subtypes of NECs.

Conclusion

Substantial clinical heterogeneity is observed for both G2 and G3 NENs. Analysis of this large national database (RGETNE) suggests that tumor morphology is a relevant aid to further stratify prognosis of patients with GEP-NENs, beyond the proliferation index. In addition, the proliferation rate behaves as a continuous variable illustrating a biological continuum, and further subdivision of grading may also help to more accurately predict patient outcome. Nevertheless, as data are still limited, it is advisable that pathologists continue to report the precise mitotic count or Ki-67 index together with grade, as well as classical histological features including cell size (large vs. small cell) and tumor differentiation. Collaborative efforts, such as the European Neuroendocrine Tumor Society Tumor Registry initiative, are also greatly encouraged in this regard in order to generate more solid evidence to definitively address these issues.

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Disclosures

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