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Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE)

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Background: Neuroendocrine tumors (NETs) are an unusual family of neoplasms with a wide and complex spectrum of clinical behavior. Here, we present the first report of a National Cancer Registry of gastroenteropancreatic neuroendocrine tumors from a Southern European country.

Patients and methods: Data was provided online at www.retegep.net by participating centers and assessed for internal consistency by external independent reviewers.

Results: The study cohort comprised 907 tumors. The most common tumor types were carcinoids (55%), pancreatic nonfunctional tumors (20%), metastatic NETs of unknown primary (9%), insulinomas (8%) and gastrinomas (4%). Forty-four percent presented with distant disease at diagnosis, most often those from small intestine (65%), colon (48%), rectum (40%) and pancreas (38%), being most unusual in appendix primaries (1.3%). Stage at diagnosis varied significantly according to sex, localization of primary tumor, tumor type and grade. Overall 5-year survival was 75.4% (95% confidence interval 71.3% to 79.5%) and was significantly greater in women, younger patients and patients with hormonal syndrome and early stage or lower grade tumors. Prognosis also differed according to tumor type and primary tumor site. However, stage and Ki-67 index were the only independent predictors for survival.

Conclusion: This national database reveals relevant information regarding epidemiology, current clinical practices and prognosis of NETs in Spain, providing valuable insights that may contribute to understand regional disparities in the incidence, patterns of care and survival of this heterogeneous disease across different continents and countries.

Key words: gastrointestinal, neuroendocrine tumors, pancreatic, registry, survival, treatment

introduction

Neuroendocrine tumors (NETs) comprise a heterogeneous family of neoplasms with a wide and complex spectrum of clinical behavior [1, 2]. They originate in a great diversity of tissues and are characterized by their ability to produce different peptides that cause distinct hormonal syndromes. However, many are clinically silent until late advanced disease. Although they are generally more indolent than carcinomas, they often have unpredictable biological behavior and are on occasions associated with a very aggressive clinical course. Recent international efforts are helping to improve the prognostic classifications of this type of tumors and to better tailor therapeutic strategies in these patients [3–6].

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The incidence of NETs ranges from 2.5 to 5 cases per 100 000 in Caucasian population [7–10]. The reported incidence has substantially increased over the last decades, partially due to improved diagnostic techniques and clinical awareness. However, incidence rates overall and per individual anatomic site are widely variable in the literature. Many issues may account for these discrepancies, including differences in patient selection, specific institutional or registration biases, racial disparities and other as yet unknown genetic and environmental factors. These issues along with patterns of care may greatly differ across countries and may ultimately influence outcome in a significant way.

To provide information regarding demographic characteristics, diagnostic procedures, tumor features, therapeutic interventions and survival of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs), a national tumor registry was launched in 2001 by GETNE, the Spanish Scientific Society of Neuroendocrine Tumors. We present here the results of this broad-based multi-institutional registry that comprises 46 academic and community sites representing all regions of Spain. To date, published data mostly refer to United States, UK and Northern European populations [7–15]. This is to our knowledge the first study providing information on this type of tumors from a Southern European country.

patients and methods

The study population was obtained from the National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors (RGETNE). RGETNE was launched by the scientific society GETNE, which is composed by specialists from multiple disciplines (oncologists, 77%; endocrinologists, 18%; surgeons, 4%; pathologists; biologists; …) and leads at the national level multiple educational and research projects on NETs. This broad-based multi-institutional registry comprises 46 academic and community sites representing all regions of Spain (Appendix 1). Data collection was provided online at www.retegep.net by investigators or study nurses from participating institutions and assessed for internal consistency by external independent reviewers. The registry database and standard operating procedures were approved by a National Scientific and Ethics Committee.

From June 2001 through December 2008, 907 tumors from 887 patients were prospectively registered. Only patients with survival data have been included in this report (855 tumors and 837 patients). The medical records were systematically reviewed to collect the following data: age, gender, functional syndrome, familial hereditary syndrome, diagnostic procedures, localization of the primary tumor, histopathological features (World Health Organization classification [16], immunohistochemical staining, grade and vascular invasion), tumor stage at diagnosis, therapeutic interventions and outcomes (surgery, local–regional therapies, hormone therapy, chemotherapy, radiotherapy and radionuclide therapy), date of diagnosis, date of relapse or disease progression, date of last visit or death and cause of death. Tumor stage was classified as localized (confined to the organ of origin), regional (invasion of surrounding organs or tissues or regional lymph nodes) or distant (spread to distant organs). Number (i.e. single or multiple) and size of primary tumors and specific sites of distant metastasis were also recorded.

Descriptive statistics were used to characterize the most relevant clinical parameters. The association of categorical variables was assessed by the chi-square test or Fisher's exact test when appropriate. One-way analysis of variance was used for comparison of continuous variables between groups. Overall survival was defined as the time elapsed from the date of diagnosis to the date of death from any cause or last follow-up in alive patients. Survival was estimated according to the Kaplan–Meier product limit method, and differences observed among patient subgroups were assessed by the log-rank test. Multivariate analyses using the Cox proportional hazards model were carried out to identify factors independently associated with prognosis. Gender, age, hormonal syndrome, stage, Ki-67, tumor type and localization of primary tumor were included as covariates in the model. Two-sided P values were computed; $P < 0.05$ was considered statistically significant. All analyses were carried out using the SPSS statistical package (SPSS version 16.0 for Windows; SPSS Inc., Chicago, IL).

results

patient population

Of 837 assessable patients with GEP-NETs, 458 (55%) were men and 379 (45%) were women. The median age at diagnosis was 59 years (range 10–99 years), and 25% presented with hormone hypersecretion symptoms, with no significant differences according to gender (Table 1). Appendix primaries and functional tumors were diagnosed at younger ages (median age at diagnosis: appendix primary, 42 years; insulinoma, 48 years and gastrinoma, 52 years). Multiple endocrine neoplasia was diagnosed in 43 patients (5%). Of them, 91% had hyperparathyroidism, 42% pituitary adenomas, 23% adrenal adenomas and 5% pheochromocytomas. Both adrenal adenomas (30% versus 17%) and pheochromocytomas (10% versus 0%) were more commonly observed in men as compared with women.

diagnostic procedures

Incidental diagnosis occurred in 22% of cases. The most commonly carried out imaging studies included computed tomography (CT) scan, ultrasound and somatostatin receptor scintigraphy (octreotide scintigraphy). CT scan was the procedure with the highest yield of tumor detection (75%). Octreoscan® was done in 49% of patients and 81% of them were positive. Only about one-third of the registered patients underwent endoscopic procedures. Biochemical tests such as serum chromogranin A or urinary 5-hydroxyindole acetic acid (5-HIAA) levels were only done in 41% and 27% of the population and were increased in 67% and 45% of tested patients, respectively. Immunohistochemical staining for chromogranin and synaptophysin was done in 66% and 50% of tumors, being positive in 93% and 96% of reported cases, respectively. Ki-67 index was carried out in only 36% of tumors. Other diagnostic procedures are summarized in Table 2.

tumor characteristics

The most common tumor types were gastrointestinal carcinoids (55%), followed by pancreatic nonfunctional tumors (20%) and metastatic NETs of unknown primary (9%) (Table 3). Among functional tumors, enteric carcinoids (10%), insulinomas (8%) and gastrinomas (4%) were the most commonly encountered. Glucagonomas, vasoactive intestinal peptidomas (VIPomas) or somatostatinomas were found in <2% of the population. The gastrointestinal tract was the primary tumor site in 400 patients (47%), the pancreas in 288

Table 1. Characteristics of study population ($N = 837$ patients)

	All patients, *n* (%)	Men, *n* (%)	Women, *n* (%)
Age (years)			
Median (range)	59 (10–99)	59 (16–86)	60 (10–99)
Gender			
Men	458 (54.7)		
Women	379 (45.3)		
Hormonal Syndrome	210 (24.6)	113 (24.1)	97 (25.1)
Incidental diagnosis	187 (21.9)	103 (22.0)	84 (21.7)
Histological diagnosis	772 (92.2)	422 (91.1)	350 (92.3)
MEN syndrome	43 (5.0)	20 (4.3)	23 (5.9)
Parathyroid hyperplasia	39 (90.7)	18 (90.0)	21 (91.3)
Pituitary adenoma	18 (41.9)	8 (40.0)	10 (43.5)
Adrenal adenoma	10 (23.3)	6 (30.0)	4 (17.4)
Lipoma	3 (7.0)	2 (10.0)	1 (4.3)
Pheochromocytoma	2 (4.7)	2 (10.0)	0 (0.0)
Genetic test carried out	57 (6.7)	21 (4.5)	36 (9.3)
Stage at diagnosis			
Local	311 (36.4)	149 (31.8)	162 (41.9)
Regional	121 (14.2)	70 (15.0)	51 (13.2)
Distant	378 (44.2)	218 (46.6)	160 (41.3)
NR	45 (5.3)	31 (6.6)	14 (3.6)
Primary tumor size (cm)			
<1	87 (10.2)	41 (8.8)	46 (11.9)
1–2	154 (18.0)	82 (17.5)	72 (18.6)
2.1–4	149 (17.4)	83 (17.7)	66 (17.1)
>4	151 (17.7)	84 (17.9)	67 (17.3)
NR	314 (36.7)	178 (38.0)	136 (35.1)
Multiple primary tumor	56 (6.7)	31 (6.8)	25 (6.6)
Other NETs	17 (2.0%)	9 (2.0)	8 (2.1)
Localization of metastases			
Liver	360 (42.1)	202 (43.2)	158 (40.8)
Lymph nodes	87 (10.2)	51 (10.9)	36 (9.3)
Peritoneum	56 (6.5)	35 (7.5)	21 (5.4)
Bone	46 (5.4)	30 (6.4)	16 (4.1)
Lung	28 (3.3)	21 (4.5)	7 (1.8)
CNS	4 (0.5)	3 (0.6)	1 (0.3)
Adrenal	4 (0.5)	3 (0.6)	1 (0.3)

MEN, multiple endocrine neoplasia; NR, not reported; NETs, neuroendocrine tumors; CNS, central nervous system.

Table 2. Diagnostic procedures

	Cases tested	Elevated or positive tests	
Biochemical tests			
$n = 837$ patients		*n*	%
5-hydroxyindole acetic acid	351	157	44.7
Chromogranin	234	156	66.7
Gastrin	183	73	39.9
Serotonin	112	67	59.8
Insulin	149	57	38.3
Glucagon	98	18	18.4
VIP	54	16	29.6
PP	52	11	21.2
ACTH	52	9	17.3
PTH-RP	24	7	29.2
Immunohistochemistry			
$n = 855$ tumors		*n*	%
Chromogranin	563	521	92.5
Synaptophysin	427	409	95.8
Enolase	241	227	94.2
Insulin	128	35	27.3
Gastrin	121	31	25.6
Glucagon	125	42	33.6
Serotonin	51	19	37.3
Somatostatin	113	21	18.3
Imaging studies			
$n = 837$ patients		*n*	%
Ultrasound	406	341	84.0
CT scan	720	644	89.4
MR	168	156	92.9
PET	29	24	82.8
Octreoscan®	418	342	81.8
Oral endoscopy	243	158	65.0
Colonoscopy	225	147	65.3
Echoendoscopy	65	58	89.2
Angiography	36	29	80.6
Exploratoy laparotomy	171	166	97.1
Intraoperative ultrasound	49	44	89.8
Bronchoscopy	19	8	42.1

VIP, vasoactive intestinal peptide; PP, pancreatic polypeptide; ACTH, adrenal corticotrophin; PTH-RP, parathormone-related peptide; CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography.

patients (34%) and in 167 patients (20%), primary tumor site was unknown or not registered. Among enteric tumors, small intestine (16%), appendix (9%) and stomach (6%) were the most frequent sites of origin. Neither the distribution of tumor types nor primary tumor localizations varied significantly by gender, although there was a slightly higher incidence of insulinomas in women and of colon primary tumors in men (Table 3).

At diagnosis, tumors were localized in 36% of the patients, had regional spread in 14% and had distant metastases in 44%. Over one-third of them had tumors >2 cm (17% >4 cm). Fifty-six patients (7%) presented multiple primary tumors and 17 (2%) had several NET types. Ki-67 index was <2% in 44% of assessed tumors and >20% in 18%. The most common site of distant metastases was liver (42%), followed by distant lymph nodes (10%), peritoneum (7%), bone (5%) and lung (3%).

Women tended to have earlier tumor stages than men (42% versus 32% had localized disease). Stage at diagnosis was also significantly different depending upon localization of primary tumor, tumor type and grade (Table 4). The primary tumor sites that presented most frequently with distant disease at diagnosis included small intestine (65%), colon (48%), rectum (40%) and pancreas (38%), whereas it was most unusual in appendix primaries (1.3%). The tumor types most commonly associated with widespread disease were VIPomas (71%), pancreatic nonfunctioning tumors (44%) and bowel carcinoids (41%), as opposed to gastrinomas (22%), insulinomas or glucagonomas (15% each). As expected, poorly differentiated tumors were more prone to have distant metastasis at diagnosis (67%), although the proportion of patients with

Table 3. Tumor characteristics ($N = 855$ tumors)

	All patients		Men,	Women,
	N	%	*n* (%)	*n* (%)
Tumor type				
Carcinoid enteric tumor	466	54.5	267 (57.1)	199 (51.4)
Pancreatic nonfunctional NET	171	20.0	95 (20.3)	76 (19.6)
Metastasis of unknown primary	78	9.1	40 (8.5)	38 (9.8)
Insulinoma	67	7.8	31 (6.6)	36 (9.3)
Gastrinoma	37	4.3	21 (4.5)	16 (4.1)
Glucagonoma	13	1.5	5 (1.1)	8 (2.1)
Pancreatic NET with ectopic HP	12	1.4	5 (1.1)	7 (1.8)
VIPoma	7	0.8	3 (0.6)	4 (1.0)
Pancreatic-mixed NET	3	0.4	1 (0.2)	2 (0.5)
Somatostatinoma	1	0.1	0 (0.0)	1 (0.3)
Primary tumor site				
Pancreas	288	33.7	147 (31.4)	141 (36.4)
Gastrointestinal tract	400	46.8	228 (48.7)	172 (44.4)
Stomach	51	6.0	29 (6.2)	22 (5.7)
Duodenum	30	3.5	17 (3.6)	13 (3.4)
Jejunum–ileum	133	15.6	71 (15.2)	62 (16.0)
Appendix	80	9.4	42 (9.0)	38 (9.8)
Colon	40	4.7	29 (6.2)	11 (2.8)
Rectum	50	5.8	29 (6.2)	21 (5.4)
Enteric NOS	16	1.9	11 (2.4)	5 (1.3)
Unknown or not registered	167	19.5	93 (19.9)	74 (19.1)
Histopathological features				
Ki-67 (%)				
<2	135	15.8	70 (15.0)	65 (16.8)
3–20	115	13.5	59 (12.6)	56 (14.5)
>20	54	6.3	34 (7.3)	20 (5.2)
NR	551	64.4	305 (65.2)	246 (63.6)
Vascular invasion				
Yes	171	20.0	91 (19.4)	80 (20.7)
No	236	27.6	120 (25.6)	116 (30.0)
NR	448	52.4	257 (54.9)	191 (49.4)
Lymphatic invasion				
Yes	157	18.4	88 (18.8)	69 (17.8)
No	209	24.4	104 (22.2)	105 (27.1)
NR	489	57.2	276 (59.0)	213 (55.0)
Perineural invasion				
Yes	106	12.4	65 (13.9)	41 (10.6)
No	247	28.9	118 (25.2)	129 (33.3)
NR	502	58.7	285 (60.9)	217 (56.1)

NET, neuroendocrine tumors; HP, hormone production; VIPoma, vasoactive intestinal peptidoma; NOS, not otherwise specified; NR, not reported.

well-differentiated tumors and stage IV disease at presentation was also rather high (38%).

therapeutic interventions

Overall, about two-thirds of the patients underwent surgery, most of them with curative intent (65%) but also with palliative purposes (14%). The proportion was higher among patients with local (85%) or regional (95%) disease but still remarkable in patients with widespread tumors (48%). Surgical resection of the primary tumor was carried out in 84% and 45% of patients with local versus distant disease, respectively. One hundred and twenty-nine patients underwent resection of metastatic disease: 27 patients had surgery of metachronous and 92 of synchronous metastases (Table 5). Local–regional therapies such as embolization, chemoembolization, radiofrequency or other ablative techniques were uncommon (<5% of the population).

Three hundred and seventy-two patients (44%) received some kind of systemic therapy at some point along the course of the disease: 29% received somatostatin analogues, 9% interferon and 25% chemotherapy. These percentages were substantially higher among patients that presented with advanced disease (51% somatostatin analogues, 17% interferon and 41% chemotherapy). The somatostatin analogue most commonly used was octreotide (30% of patients versus 14% lanreotide). The cytotoxic drugs most frequently employed were platinum compounds (113 patients, 18.1%), etoposide (99 patients, 15.8%), streptozotocin (91 patients, 14.6%), fluoropyrimidines (88 patients, 14.1%), anthracyclines (53 patients, 8.5%), taxanes (15 patients, 2.4%), gemcitabine (10 patients, 1.6%), topoisomerase I inhibitors (7 patients, 1.1%), dacarbazine–temozolomide (4 patients, 0.6%) and mTOR inhibitors and antiangiogenics (4 patients each, 0.6%). The most common chemotherapy combination regimens used as first-line therapy included platinum–etoposide (93 patients, 14.9%), streptozotocin–5-fluorouracil (5-FU) (50 patients, 8.0%), doxorubicin–streptozotocin (37 patients, 5.9%), doxorubicin/5-FU (2 patients, 0.3%), doxorubicin–streptozotocin–5-FU (3 patients, 0.5%), oxaliplatin–fluoropyrimidine (6 patients, 1.0%), paclitaxel–carboplatin (6 patients, 1.0%) and docetaxel–gemcitabine (4 patients, 0.6%).

survival and prognostic factors

At the last follow-up, 157 patients had died (19%). The median overall survival for all registered patients was 12 years (range 0.1–24.8 years), with 75.5% of patients alive at 5 years (95% confidence interval 71.4% to 79.6%). The main causes of death were tumor related (77%), treatment related (7%), due to other neoplasia (3%) or due to medical complications unrelated to tumor or therapy (12%). Sixty-one patients (7%) developed other non-neuroendocrine malignant neoplasia, which included 28 gastrointestinal tumors (22 colorectal, 4 biliopancreatic and 1 gastric adenocarcinomas), 15 genitourinary malignancies (5 urothelial carcinomas, 4 prostate adenocarcinomas, 4 clear-cell renal carcinomas, 1 Sertoli cell testicular tumor and 1 penis carcinoma), 9 gynecological cancers (3 breast, 3 ovarian, 2 endometrial and 1 cervical carcinomas), 4 head and neck tumors (1 meningioma, 1 neurinoma, 1 laryngeal and 1 follicular thyroid carcinoma), 3 hematological malignancies (1 multiple myeloma, 1 lymphoma and 1 leukemia) and a liposarcoma. Overall survival was significantly greater in women, younger patients and patients with hormonal syndrome and in early stage or lower grade tumors (Table 6) (Figure 1). Prognosis also differed

Table 4. Stage at diagnosis according to localization of primary tumor, tumor type and grade

	Stage at diagnosis			
	All patients, *n*	Local, *n* (%)	Regional, *n* (%)	Distant, *n* (%)
Tumor type				
Carcinoid enteric tumor	466	177 (38.0)	71 (15.2)	192 (41.2)
Pancreatic nonfunctional NET	171	59 (34.5)	32 (18.7)	75 (43.9)
Metastasis of unknown primary	78	0 (0.0)	0 (0.0)	77 (98.7)
Insulinoma	67	49 (73.1)	4 (6.0)	10 (14.9)
Gastrinoma	37	14 (37.8)	12 (32.4)	8 (21.6)
Glucagonoma	13	7 (53.8)	2 (15.4)	2 (15.4)
Pancreatic NET with ectopic HP	12	4 (33.3)	0 (0.0)	6 (50.0)
VIPoma	7	1 (14.3)	0 (0.0)	5 (71.4)
Pancreatic-mixed NET	3	0 (0.0)	0 (0.0)	3 (100)
Somatostatinoma	1	0 (0.0)	0 (0.0)	0 (0.0)
Primary tumor site				
Pancreas	288	121 (42.0)	47 (16.3)	109 (37.8)
Gastrointestinal tract	400	167 (41.8)	68 (17.0)	148 (37.0)
Stomach	51	30 (58.8)	10 (19.6)	11 (21.6)
Duodenum	30	14 (46.7)	5 (16.7)	11 (36.7)
Jejunum–ileum	133	13 (9.8)	32 (24.1)	86 (64.7)
Appendix	80	69 (86.3)	6 (7.5)	1 (1.3)
Colon	40	9 (22.5)	12 (30.0)	19 (47.5)
Rectum	50	27 (54.0)	3 (6.0)	20 (40.0)
Enteric NOS	16	5 (31.3)	0 (0.0)	0 (0.0)
Unknown or not registered	167	23 (13.8)	6 (3.6)	121 (72.5)
Histopathological features				
Ki-67 (%)				
<2	135	55 (40.7)	24 (17.8)	56 (41.5)
3–20	115	29 (25.2)	20 (17.4)	66 (57.4)
>20	54	9 (16.7)	13 (24.1)	32 (59.3)
NR	551	218 (39.6)	64 (11.6)	224 (40.7)
Tumor grade				
Well differentiated	435	197 (45.3)	71 (16.3)	167 (38.4)
Poorly differentiated	94	13 (13.8)	17 (18.1)	63 (67.0)
NR	326	101 (31.0)	33 (10.1)	148 (45.4)

NET, neuroendocrine tumors; HP, hormone production; VIPoma, vasoactive intestinal peptidoma; NOS, not otherwise specified; NR, not reported.

significantly according to tumor type (insulinoma/gastrinoma > glucagonoma/VIPoma > carcinoid/nonfunctional pancreatic tumor > metastasis of unknown primary) or to localization of primary tumor (appendix > duodenum > jejunum–ileum > pancreas > colon > rectum > stomach) (Table 6). Survival rates according to disease stage for different tumor types and primary tumor locations are provided in Table 7. Multivariate analysis confirmed stage and Ki-67 index as the only independent prognostic factors for survival (Table 8).

discussion

This study is relevant as it is to our knowledge the first providing comprehensive information on the incidence, management and outcome of this type of tumors from a Southern European country. Indeed, most reported data to date refer to the USA population and some Northern or Central European countries. As racial composition and other genetic and environmental factors, as well as availability of health care resources and institutional and registration biases may greatly differ among different patient populations, the present study may provide valuable insights which may help understand regional disparities in epidemiology, patterns of care and survival of NETs across different continents and countries.

This study confirms that NETs are a broad family of tumors with a wide range of clinical presentations and outcomes. Although more indolent than carcinomas, indeed the overall survival of our series was 75% at 5 years, the prognosis was highly variable from 100% for appendix primaries to <30% for poorly differentiated tumors. There was a slight preponderance of males in our series (versus a slight women preponderance in other series) [7, 8], although sex ratio was close to 1. As expected, the gastrointestinal tract was the primary tumor site in 400 patients (47%), the pancreas in 288 patients (34%) and in 167 patients (20%), primary tumor site was unknown or not registered. However, among enteric carcinoids, primary tumor site distribution in our series significantly differed with that observed in the Surveillance, Epidemiology and End Results (SEER) Program tumor registry. While the rectum was the most common gastrointestinal tumor primary in the USA

Table 5. Therapeutic interventions ($N = 837$ patients)

	Stage at diagnosis			
	All patients, *n* (%)	Local, *n* (%)	Regional, *n* (%)	Distant, *n* (%)
Surgery	575 (68.7)	264 (84.9)	115 (95.0)	180 (47.62)
Primary tumor	559 (71.6)	262 (84.2)	115 (95.0)	169 (44.7)
Metastasis	129 (15.4)	12 (3.9)	15 (12.4)	92 (24.3)
Curative	545 (65.1)	263 (84.6)	112 (92.6)	155 (41)
Palliative/cytoreductive	118 (14.1)	5 (1.6)	5 (4.1)	103 (27.2)
Embolization	10 (1.2)	0 (0.0)	2 (1.7)	7 (1.9)
Chemoembolization	23 (2.7)	2 (0.6)	0 (0.0)	20 (5.3)
Ablative therapies	20 (2.4)	2 (0.6)	1 (0.8)	17 (4.5)
Radiotherapy	27 (3.2)	3 (1.0)	3 (2.5)	21 (5.6)
Radionuclides	8 (1)	0 (0.0)	1 (0.8)	7 (1.9)
Pharmacotherapy	372 (44.4)	42 (13.5)	39 (32.2)	279 (73.8)
Somatostatin analogues	243 (29)	22 (7.1)	22 (18.2)	193 (51.1)
Chemotherapy	209 (25)	24 (7.7)	24 (19.8)	155 (41)
Interferon	79 (9.4)	5 (1.6)	4 (3.3)	64 (16.9)

population, particularly in Asian/Pacific Islander, American Indian/Alaskan Native and African-American patients, in our cohort, the most frequent sites of origin were the small intestine followed by the appendix and stomach, whereas the rectum only accounted for 6% of tumor cases [7]. Registries from Northern European countries, which as Spain have predominantly white Caucasian population, also find small intestine as the most common primary site of intestinal NETs [8].

A significant proportion of patients (44%) in our national registry presented with widespread disease at diagnosis compared with other series (21% in SEER database). Several potential explanations may justify this difference. First of all, the fact that the great majority of GETNE Society members (77%) are medical oncologists may introduce some registration bias as they generally deal with more advanced cases than endocrinologists, gastroenterologists or surgeons. On the other hand, a notably high proportion of patients in the SEER Registry had unknown stage (20%) versus only 5% in our series [7]. Nevertheless, a later diagnosis in our country possibly caused by poorer availability of health care resources cannot be excluded and is of concern particularly in this disease where surgery is the primary means of cure. However, this hypothesis is not consistent with the fact that despite more advanced disease, the overall survival of our cohort is in the upper range of that previously reported in other series. Stage migration due to improved diagnostic techniques, which would be expected in a more recent series like ours, could potentially explain these observations.

A strong correlation was observed, as in the SEER Registry, between primary tumor site and disease stage. However, some discrepancies in this association between both series shall be remarked. Whereas in our cohort, the most common primary tumor sites associated with widespread disease at diagnosis were jejunum/ileum (65%), colon (48%) and rectum (40%); in the SEER Registry, these included pancreas (64%), cecum/colon (44%/32%) and jejunum/ileum (30%). Early-stage gastric and rectal tumors are likely underrepresented in the Spanish registry as there is a low participation of gastroenterologists in the National Scientific Society of Neuroendocrine Tumors (GETNE). Tumor type was also significantly associated with stage at diagnosis: a higher proportion of VIPomas (71%), pancreatic nonfunctional tumors (44%) and enteric carcinoids (41%) presented with stage IV disease, compared with gastrinomas (22%), insulinomas or glucagonomas (15% each). As expected, poorly differentiated tumors were more prone to have distant metastases at diagnosis (67%), although the proportion of patients with well-differentiated tumors and stage IV disease at presentation was also rather high (38%). Finally, a trend toward a more localized disease and improved survival was observed in women.

The present study also provides one of the most comprehensive reports on diagnostic and therapeutic procedures used in current clinical practice in this patient population. Of note, specific biochemical tests or immunohistochemical stainings were greatly infra-utilized. Although the high rate of incidental diagnosis (22%) may partially explain why only 41% and 27% of patients had serum chromogranin A or urinary 5-HIAA levels tested at diagnosis, a low use of immunohistochemical staining for chromogranin, synaptophysin and Ki-67 index, which were only carried out in 66%, 50% and 36% of tumors, respectively, was also observed. These figures probably reflect the low referral rate of patients to specialized centers in our country. Regarding therapeutic interventions, however, there was an extensive and appropriate use of surgery and systemic therapies in all disease stages, although a low use of local–regional ablative approaches again most likely reflecting a low number of referrals. The nonavailability of radionuclide therapy in Spain justifies the fact that only 1% of the patients received this therapeutic modality.

Overall prognosis was favorable, with a 5-year survival rate of 75%. This figure, however, may be somewhat overestimated due to insufficient follow-up in the context of a slow growing disease with a high rate of late events. Indeed, despite the relatively indolent nature of these tumors, as compared with gastrointestinal carcinomas, once the tumor has progressed

Table 6. Overall survival

	Overall survival (years)				
	n	Median	% at 5 years	95% CI	*P*
All patients	766	12.1	75.5	71.4–79.6	
Sex					0.022
Men	415	11.7	74.4	67.9–79.9	
Women	351	NR	76.9	70.8–83.0	
Age (years)					0.012
<30	33	NR	100	NC	
31–60	331	NR	88.0	82.9–93.1	
>60	325	NR	79.6	73.7–85.5	
Hormonal syndrome					0.007
Yes	176	12.1	87.1	81.0–93.1	
No	590	13.8	71.2	66.1–76.3	
MEN syndrome					0.053
Yes	32	NR	100	NC	
No	685	12.1	75.1	70.8–79.4	
UK	49	9.2	65.4	47.8–83.0	
Stage at diagnosis					<0.001
Local	277	13.8	90.1	84.0–96.2	
Regional	118	NR	82.9	73.9–91.9	
Distant	344	6.5	60.4	53.3–67.5	
Tumor type					<0.001
Carcinoid enteric tumor	422	12.1	77.6	72.1–83.1	
Pancreatic nonfunctional NET	162	NR	71.1	61.1–81.1	
Metastasis of unknown primary	69	4.2	45.3	26.7–63.9	
Insulinoma	55	NR	88.7	77.7–99.7	
Gastrinoma	28	NR	96.2	88.8–100	
Glucagonoma	11	6.9	80.0	55.3–100	
Pancreatic NET with ectopic HP	9	8.3	75.0	45.0–100	
VIPoma	6	NR	75.0	32.5–100	
Pancreatic-mixed NET	3	2.7	50	0.0–100	
Somatostatinoma	1	9.6	100	NC	
Primary tumor site					<0.001
Pancreas	265	NR	78.1	71.2–85.0	
Gastrointestinal tract	372	NR	80.4	74.9–85.9	
Stomach	46	NR	61.4	38.5–84.3	
Duodenum	25	NR	89.3	75.2–100	
Jejunum–ileum	126	11.7	83.0	73.8–92.2	
Appendix	73	NR	100	NC	
Colon	39	NR	65.1	48.4–81.8	
Rectum	48	12.1	64.1	45.1–83.1	
Enteric NOS	15	9.2	83.6	62.4–100	
UK or not registered	129	6.5	56.7	44.6–68.9	
Histopathological features					
Ki-67 (%)					<0.001
<2	126	11.7	83.3	68.8–97.8	
3–20	109	NR	77.1	64.0–90.2	
>20	53	1.2	43.5	25.3–61.7	
UK	478	12.1	75.8	71.1–80.5	
Tumor grade					<0.001
Well differentiated	410	NR	83.3	78.2–88.4	
Poorly differentiated	85	1.7	39.1	24.6–53.6	
UK	271	11.9	74.2	67.3–81.1	

CI, confidence interval; NR, not reached; NC, not computable; MEN, multiple endocrine neoplasia; UK, unknown; NET, neuroendocrine tumors; HP, hormone production; VIPoma, vasoactive intestinal peptidoma; NOS, not otherwise specified.

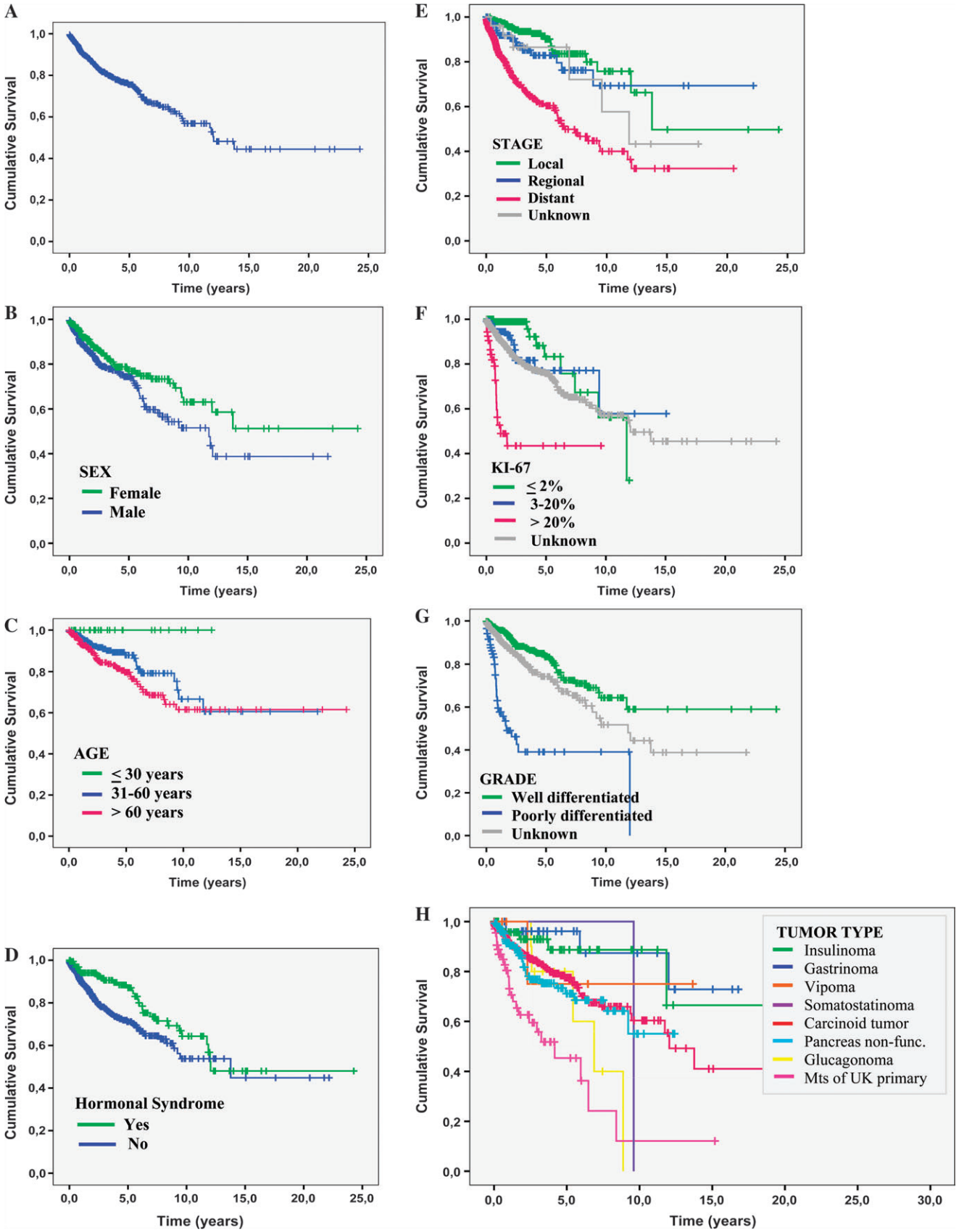

Figure 1. (A) Overall survival in all patients. (B) Overall survival by gender. (C) Overall survival by age. (D) Overall survival by hormonal syndrome. (E) Overall survival by stage of disease. (F) Overall survival by Ki-67 index. (G) Overall survival by histological grade. (H) Overall survival by tumor type.

Table 7. Survival according to primary tumor site, tumor type and stage

	Survival (% at 5 years)							
	All		Local		Regional		Distant	
	n	%	*n*	%	*n*	%	*n*	%
Tumor type								
Carcinoid enteric tumor	422	77.6	166	91.1	69	79.7	174	64.3
Pancreatic nonfunctional NET	162	71.1	54	85.3	31	83.7	72	56.4
Metastasis of unknown primary	69	45.3	0	–	0	–	69	45.3
Insulinoma	55	88.7	39	88.4	4	100	9	75.0
Gastrinoma	28	96.2	8	100	12	100	7	83.3
Glucagonoma	11	80.0	6	100	2	50.0	2	50.0
Pancreatic NET with ectopic HP	9	75.0	3	–	0	–	4	27.2
VIPoma	6	75.0	1	100	0	–	4	27.2
Pancreatic-mixed NET	3	50.0	0	–	0	–	3	35.4
Somatostatinoma	1	100	0	–	0	–	0	–
Primary tumor site								
Pancreas	265	78.1	108	89.7	46	87.0	102	60.9
Gastrointestinal tract	372	80.4	155	91.5	66	78.9	137	68.1
Stomach	46	61.4	27	87.4	10	35.6	9	0.0
Duodenum	25	89.3	10	100	5	100	10	72.9
Jejunum–ileum	126	83.0	13	100	31	74.0	80	82.4
Appendix	73	100	65	100	5	100	1	100.0
Colon	39	65.1	9	71.1	12	91.7	18	42.9
Rectum	48	64.1	26	75.0	3	66.7	19	29.8
Enteric NOS	15	83.6	5	66.7	0	–	0	–
Unknown or not registered	129	56.7	14	83.1	6	100	105	50.0

NET, neuroendocrine tumors; HP, hormone production; VIPoma, vasoactive intestinal peptidoma; NOS, not otherwise specified.

beyond surgical resectability, the disease is eminently incurable. In this regard, it is remarkable that 77% of deaths in our cohort were due to tumor progression and an additional 7% were due to treatment-related issues (drug toxicity, surgical complications). Survival was significantly greater in women, younger patients and patients with hormonal syndrome and in early stage or lower grade tumors. As observed by others, prognosis also differed significantly according to tumor type or to primary tumor site, although with some striking differences compared with other geographical regions (i.e. poorer survival for gastric or rectal primaries in our country). However, stage and grade remained the only independent predictors for outcome in multivariate analysis, which underscores the need for earlier diagnosis and for improved systemic therapies for advanced disease.

This national database reveals relevant information regarding current clinical practices and provides valuable insights into the epidemiology and outcome of this heterogeneous and not so uncommon disease. Indeed, GEP-NETs are more prevalent and lethal than previously thought. Despite some recent progress

Table 8. Cox multivariate analysis for overall survival ($N = 659$ patients)

Variable	Hazard risk	95% CI	*P*
Stage at diagnosis	3.96	1.97–7.96	0.0001
Ki-67	6.69	1.96–22.88	0.008

Variables included in the regression model: gender (men versus women), age (<30 versus 31–60 versus >60 years), hormonal syndrome (yes versus no), MEN syndrome (yes versus no versus unknown), stage at diagnosis (distant versus localized), tumor type (enteric carcinoids, pancreatic nonfunctional NET, metastasis of unknown primary, insulinomas, gastrinomas, glucagonoma, pancreatic NET with ectopic HP, VIPoma, pancreatic-mixed NET and somatostatinoma), primary tumor site (pancreas versus stomach versus duodenum versus jejunum–ileum versus appendix versus colon versus rectum versus enteric NOS), tumor grade (well versus poorly differentiated) and Ki-67 (>20% versus ≤2%). Only significant variables are given in the table.
CI, confidence interval; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumors; HP, hormone production; VIPoma, vasoactive intestinal polypeptidoma; NOS, not otherwise specified.

[17–22], patient survival has not significantly changed over the last 30 years. Improving our understanding of the molecular basis of this disease, as well as the mechanisms involved in response and resistance to therapy, will be essential tools that will help us develop early diagnosis tools and newer more rationally designed treatment strategies that will potentially change the natural history of malignant NETs. Finally, encouraging physicians to refer these patients to specialized centers and patients to participate in clinical trials is of utmost importance.

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disclosure

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appendix 1: list of participating centers and physicians in order of contribution (after authors of this paper)

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