RESEARCH

Pancreatic neuroendocrine neoplasms: survival trend analysis of a comprehensive center

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Abstract

Objectives: Therapeutic options for pancreatic neuroendocrine neoplasia (Pan-NEN) have increased over the last decade. We aim to understand the evolution of the prognosis of patients with diagnosis of Pan-NEN within a 12-year period, considering the implementation of new treatments.

Methods: This study is a retrospective cohort study of patients diagnosed with Pan-NENs between 2006 and 2017. Survival outcome estimates were calculated by Kaplan–Meier method. The impact of baseline clinicopathological characteristics on survival was explored with the use of Cox proportional hazard model.

Results: Of the 97 patients, 77 (79.9%) had well-differentiated neuroendocrine tumor (NET) according to WHO 2010 classification, and 52 (53.6%) had localized or locoregional disease. There were no differences between clinicopathological characteristics and survival outcomes when comparing patients diagnosed between 2006–2011 and 2012–2017. Neuroendocrine carcinoma – HR 2.76, 95% CI 1.17–6.55 – and stages III and IV at diagnosis were independent poor prognostic factors – HR 6.02, 95% CI 2.22–16.33 and HR 6.93, 95% CI 2.94–16.32, respectively.

Conclusions: The new therapeutic approaches did not induce better survival outcomes on Pan-NEN in recent years. This is possibly due to the indolent nature of NET grades 1 and 2, even metastatic, allowing patients to be submitted to new target therapies along their disease course.

Introduction

Incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) has been steadily rising both in the United States and in Europe, with a 6.5-fold increase in incidence observed over the past four decades (Fraenkel *et al.* 2014, Dasari *et al.* 2017). In Europe, the incidence of GEP-NEN ranges between 1.33 and 2.33/100,000/year, depending on the data provided by regional and national registries, being highly heterogeneous (Levi *et al.* 2000, Lepage *et al.* 2004, Hauso *et al.* 2008, Fraenkel *et al.* 2014).

According to Surveillance, Epidemiology and End Results database, the current incidence of pancreatic neuroendocrine neoplasms (Pan-NEN) in United States is 0.8/100,000/year (Dasari *et al.* 2017). However, data regarding the incidence of Pan-NEN in Europe are scarce,

and only few studies have evaluated large case series of Pan-NEN, namely at national level (Santos *et al.* 2009, Fraenkel *et al.* 2014). Representing 1–2% of all pancreatic tumors, Pan-NENs are heterogeneous neoplasms, with a wide range of clinical manifestations depending on the disease stage and their ability to cause hormonal syndromes (Oberg & Eriksson 2005, Asa 2011, Ito *et al.* 2015). In 2017, the World Health Organization (WHO) set a new classification of Pan-NENs as neuroendocrine tumors (NET) grades 1, 2, and 3 and neuroendocrine carcinoma (NEC) based on proliferation (mitotic count and Ki-67 index), tumor histomorphology, and molecular biomarkers, replacing the WHO 2010 classification (Bosman *et al.* 2010, Nagtegaal *et al.* 2020).

Knowledge about biology and recent discoveries of the applicability of new therapeutic modalities (oral chemotherapy, radionuclide therapy, target therapies) in Pan-NENs have increased the therapeutic armamentarium, particularly in the metastatic setting (Yao *et al.* 2011, Faivre *et al.* 2017). However, the effect of implementing these therapies in the context of metastatic/irresectable disease in the real world is still poorly understood, with infrequent publishing of large series.

In this context, our primary objective is to understand the survival outcomes of patients with Pan-NENs diagnosis within a 12-year period, considering the implementation of new therapeutic strategies. We also aim to evaluate the clinical features and treatment strategies of Pan-NENs patients treated at the Portuguese largest Comprehensive Cancer Center and to ascertain the prognostic factors according to the baseline clinicopathological characteristics of Pan-NENs.

Materials and methods

Study design

We performed a retrospective cohort study of patients diagnosed with Pan-NENs between January 2006 and December 2017 and admitted for treatment at Portuguese Oncology Institute of Oporto (IPOP). Patient inclusion criteria included (i) adult patients, aged ≥18 years old, (ii) with a histologic or cytologic diagnosis of NEN, and (iii) with tumor primary topography in the pancreas. Patients were excluded if (i) their histologic or cytologic sample had the presence of other malignant histology (mixed tumors), (ii) had an unknown primary topography or primary topography outside the pancreas, or (iii) were not being followed at IPOP.

Patients were retrieved from the Cancer Registry of IPOP database using the following histology codes of the International Classification of Diseases for Oncology (ICD-O-3): 8013, 8040-8045, 8150-8157, 8240-8246, and 8249. Only identified pancreatic topography and malignant behavior (/3) were selected. Demographic data (age of diagnosis, gender), cancer diagnostic information (histology, topography within the pancreas, disease extent), patient-related information (ECOG performance status, Charlson comorbidity index (CCI), tumor-related or clinical symptoms), selected strategy of cancer treatment, and outcomes data were collected from patient medical records. Tumor grading and TNM staging were conducted according to the WHO 2010 classification and the sixth and seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system as the study was conducted between 2006 and 2017 (Rindi *et al.* 2016, Edge *et al.* 2010). Genetic syndromes were investigated according to patient's family history, past medical history, and clinical, pathological, and analytical characteristics. In order to evaluate the survival trends and the possible impact of new therapeutic modalities, we separated the Pan-NEN into two groups according to the time of diagnosis – 2006–2011 and 2012–2017 – since the implementation of those treatments was started between 2012 and 2013.

This study was approved by the Institutional Administration Board and by the Ethics Committee number CES/IPO: 66/021, and its design and conception were of the strict responsibility of the investigators.

Statistical analysis

Baseline clinical characteristics of included subjects and tumor characteristics and treatment strategies were studied using descriptive statistics as appropriate. Clinical baseline and tumor characteristics were studied and compared for NET grade 1, NET grade 2, and NEC and also between patients diagnosed with Pan-NEN at 2006–2011 and 2012–2017. Overall survival (OS) was defined as the time interval between diagnosis and patients' death by Pan-NEN or the last clinical evaluation. Progression-free survival (PFS) was defined as time from diagnosis until the date of last clinical assessment, of first disease progression, or recurrence, or death, whichever occurred first. Disease-free survival (DFS) for patients with no residual disease after curative procedure was defined as time from diagnosis until the date of last clinical assessment, of first disease recurrence, or death. Median PFS, DFS, and survival time estimates were calculated by Kaplan–Meier method. To examine

trends in patients' OS with PAN-NENs, survival was calculated separately for 2006–2011 and 2012–2017. The impact of baseline clinicopathological characteristics on survival was explored with the use of univariate analysis, and the statistically significant variables were included in the multivariate Cox proportional hazard model. For this exploratory analysis, $P < 0.05$ was considered significant. All data were analyzed using the SPSS Statistics® v24.0 and R® v3.6.3 software.

Results

### Patient and disease characteristics

Between January 2006 and December 2017, 150 patients were identified as having Pan-NEN (Fig. 1) and 53 patients were excluded – 5 had mixed histologies and 48 had no follow up at the institution (27 had been referred to our center only for peptide receptor radionuclide therapy (PRRT) and 1 to palliative radiotherapy, but they were being treated and followed at other hospitals). The final cohort of 97 patients had a median follow-up time of 47 (1–171) months.

There was a higher proportion of patients with Pan-NENs diagnosis referred to our center between 2012 and 2017 ($n = 37$, 38.1%) than between 2006 and 2011 ($n = 60$, 61.9%). Patient and tumor characteristics are described in Table 1. Median patients' age was 60 years (range 19–84), with a slight predominance of male gender (56.7%). The proportion of patients with CCI $\geq$ 3 was of 48.5% with a frequency of second non-neuroendocrine malignancies history of 28 (28.9%) – 16 patients with localized malignancy, 11 metastatic, and 1 chronic lymphocytic

leukemia – diabetes of 27 (27.8%), and arterial hypertension of 34 (35.1%). Nineteen patients met criteria for genetic testing (18 for multiple endocrine neoplasia type 1 (MEN1) and 1 for von Hippel Lindau). Of those, two were diagnosed with genetic syndrome, both with MEN1. The majority of patients were symptomatic at diagnosis, mainly due to tumor-related symptoms ($n = 55$, 69.6%), though 12 (15.0%) had hormone secretion-related symptoms. When considering functional NENs, the most predominant types were insulinomas ($n = 4$), followed by glucagonoma ($n = 3$), ACTHoma ($n = 2$), atypical carcinoid syndrome-associated tumors ($n = 2$), and gastrinoma ($n = 1$). Predominant pancreatic topography of primary tumors was body and tail ($n = 58$, 59.8%) followed by the head ($n = 29$, 29.9%).

Most tumors were well-differentiated NET grade 1 or 2 ($n = 74$, 76.3%), with the remaining being NECs. In two cases of well-differentiated NETs, it was not possible to ascertain with certainty the grade. The proportion of localized or locoregional disease at diagnosis was 53.6% ($n = 52$) and of metastatic disease was 46.4% ($n = 45$). Of patients with localized disease and treated with surgery, pathological characteristics (focality, tumor necrosis, lymphovascular, and perineural invasion) were analyzed. Multifocal tumors were identified in a minority of pathological specimens ($n = 3$, 14.3%), as well as tumor necrosis ($n = 5$, 20.0%). Lymphovascular and perineural invasion were present in 14 (41.2%) and 12 (38.5%) of the cases. Liver metastasis was the most frequent site of synchronous metastasis at diagnosis ($n = 42$, 93.3%), followed by non-regional nodal ($n = 11$, 24.4%), bone ($n = 11$, 24.4%), lung ($n = 5$, 11.1%), and peritoneum ($n = 5$, 11.1%). Metastasis in other sites constituted 11.1% ($n = 5$).
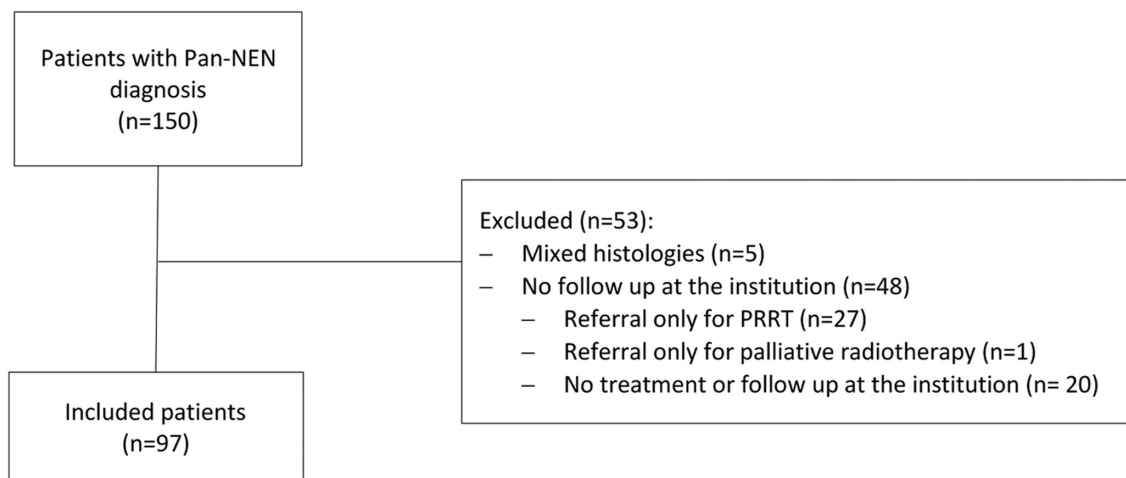
Figure 1
Overview of patients with Pan-NEN diagnosis and included in the study. PRRT, peptide receptor radionuclide therapy.

Table 1   Baseline characteristics of patients with Pan-NEN diagnosis and comparison according to the tumor grade.

WHO 2010 grade	Total ($n = 97$)	NET grade 1 ($n = 24$)	NET grade 2 ($n = 48$)	NEC ($n = 23$)	*P value*
Age – years *(*median (range))	60 (19–84)	64 (27–81)	57.5 (29–82)	60 (19–84)	0.416
Gender					
Male	55 (56.7)	15 (62.5)	24 (50)	15 (65.2)	0.389
Female	42 (43.3)	9 (37.5)	24 (50)	8 (34.8)	
ECOG PS					
<1	34 (66.7)	7 (77.8)	21(72.4)	6 (46.2)	
≥1	24 (30.4)	2 (22.2)	8 (27.6)	7 (53.8)	0.199
Unkown	46	15	19	10	
Charlson comorbidity index					
<3	50 (51.5)	11 (45.8)	25 (52.1)	13 (56.5)	0.799
≥3	47 (48.5)	13 (54.2)	23 (47.9)	10 (43.5)	
Diabetes mellitus					
No	70 (70.2)	19 (79.2)	31 (64.6)	19 (82.6)	0.199
Yes	27 (27.8)	5 (20.8)	17 (35.4)	4 (17.4)	
Arterial hypertension					
No	63 (64.9)	19 (79.2)	25 (52.1)	17 (73.9)	**0.042**
Yes	34 (35.1)	5 (20.8)	23 (47.9)	6 (26.1)	
Non-neuroendocrine malignancy (current or past history)					
No	69 (71.1)	12 (50.0)	36 (75.0)	20 (87.0)	**0.015**
Yes	28 (28.9)	12 (50.0)	12 (25.0)	3 (13.0)	
Symptoms at diagnosis					
No	19 (23.8)	8 (44.8)	6 (15.8)	4 (18.2)	
Yes	61 (76.3)	10 (55.6)	32 (84.2)	18 (81.8)	**0.048**
Unknown	17	6	10	1	
Pancreatic topography					
Body and tail	58 (59.8)	16 (66.7)	31 (64.6)	11 (47.8)	
Head	29 (29.9)	6 (25.0)	11 (22.9)	11 (47.8)	0.178
Multiple sites	1 (1.0)	1 (4.2)	0 (0.0)	0 (0.0)	
Not specified	9 (9.3)	1 (4.2)	6 (12.5)	1 (4.3)	
AJCC/UICC stage[a]					
IA/B	29 (30.9)	13 (54.2)	15 (33.3)	0 (0.0)	
IIA/B	9 (9.6)	3 (12.5)	4 (8.9)	2 (8.7)	**<0.001**
III	11 (11.7)	2 (8.3)	4 (8.9)	4 (17.4)	
IV	45 (47.9)	6 (25.0)	22 (48.9)	17 (73.9)	
Unknown, nonmetastatic	3	0	3	0	

[a]AJCC/UICC sixth and seventh edition.
NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; Pan-NEN, pancreatic neuroendocrine neoplasia.
Bold indicates statistical significance, *P* < 0.05.

Analyzing patients' baseline characteristics according to the 2010 WHO classification (Table 1), there was a higher proportion of arterial hypertension in NET grade 2 ($P = 0.042$) and of diabetes mellitus (though not statically relevant). Current or past history of non-neuroendocrine malignancy was higher in NET grade 1 tumors ($P = 0.015$). Symptomatic disease (secretory- or anatomical-related) was more frequent in NET grade 2 and NEC ($P = 0.048$). All secretory NETs were grade 2. Additionally, there was an increase in frequencies of stage IV disease when comparing NET grades 1 and 2 and NEC ($P < 0.001$). No differences were found between grades by age, gender, ECOG performance status, CCI, and pancreatic topography. There were no statistical differences in the clinical and tumor characteristics for the patients diagnosed with Pan-NEN between the time periods 2006–2011 and 2012–2017 (data not shown).

Therapeutic strategies

First-line treatment options according to treatment intention are detailed in Table 2. A total of 45 patients had been considered for curative intention treatment. Surgery of the primary tumor was the initial therapeutic strategy in 43 (95.6%) of the cases and pancreatic embolization in 1 (2.2%) case. Of the patients treated with surgery, four were subsequently treated with somatostatin analogs (SSA) and one was

Table 2 First-line treatment options according to treatment intention at diagnosis.

Treatment modality	*n* (%)	Multimodality	*n* (%)
Curative intention treatment patients at diagnosis (*n* = 45; 46.4%)			
Surgical therapy (primary tumor)	43 (95.6)	Monotherapy	40 (88.9)
Pancreatic embolization	1 (2.2)	Multimodal therapies	5 (11.1)
PRRT	1 (2.2)		
SSA	5 (11.1)		
Palliative intention treatment patients at diagnosis (*n* = 52; 53.6%)			
Best supportive care	3 (5.8)	Best supportive care	3 (5.8)
Surgical therapy	17 (32.7)	Monotherapy	21 (40.4)
TAE	10 (19.2)	Multimodal therapies	28 (53.8)
PRRT	4 (7.7)		
SSA	46 (88.5)		
Chemotherapy	20 (38.5)		

PRRT, peptide receptor radionuclide therapy; SSA: somatostatin analogs; TAE, hepatic trans-arterial embolization.

treated primarily with SSA and PRRT as it was initially considered irresectable. Of the 52 palliative patients at diagnosis (7 NET grade 1, 24 NET grade 2, 20 NEC, and 1 nondetermined), 3 (5.8%) had no antineoplastic treatment and were offered best supportive care. Two or more therapeutic antineoplastic treatments were offered to 28 patients (54.9%). Cytoreductive surgery was the first-line treatment option in 17 (32.7%) of cases (2 with primary tumor and hepatic metastasis resection and 1 patient with hepatic metastasis resection only). SSA was first-line treatment option in 46 patients (88.5%), 9 of which in monotherapy. First-line chemotherapy was performed in 20 patients (39.2%) – 3 (13.0%) and 4 (17.4%) of NET grade 2 were treated with streptozotocin/5-fluorouracil and platinum/etoposide regimens; 12 (60.0%) and 1 (0.05%) NEC with platinum/etoposide and doxorubicin/5-fluorouracil regimens. Hepatic trans-arterial embolization (TAE) was performed in 10 patients (19.2%), and 4 patients received PRRT (7.7%) as part of the initial therapeutic strategy.

Seventy-two patients had antineoplastic palliative treatments (52 metastatic/locally advanced at diagnosis, 18 after recurrence and 2 refused or were not fit to curative surgery at diagnosis), and of those, 26 (36.1%) had 2 lines and 20 (27.8%) had ≥ 3 lines of treatment. Antineoplastic treatment palliative modalities are described in detail in Table 3.

Treatment options according to the WHO 2010 classification are detailed in Fig. 2. NET grades 1 and 2 were treated with surgery whenever possible and it was the main therapeutic strategy (*n* = 17, 70.8% and *n* = 36, 75.0%, respectively). SSA, TAE, PRRT, everolimus, and chemotherapy with temozolomide and capecitabine were predominantly used in NET grade 2. As for NEC treatment modalities, chemotherapy was the most frequent option,

usually platinum based and, SSA and PRRT were occasionally used. Radiotherapy was used in the palliative context, for symptomatic control of bone and brain metastasis. There were no statistical differences in the type of treatment modalities used for patients diagnosed with Pan-NEN between the time periods 2006–2011 and 2012–2017.

Patient outcomes

A total of 18 out of 43 patients (41.8%) had disease recurrence after surgery. Most frequent sites of disease recurrence were local recurrence (*n* = 6, 33.3%), liver (*n* = 9, 50%), nodal (*n* = 6, 33.3%) and bone (*n* =3, 16.6%). Six patients had disease recurrence in two or more organs. Median DFS for localized disease after curative intent treatment was not reached, with 5-year DFS of 61.9%. Median PFS for first-line treatment was 25.0 months (95% CI 18.0–32.0), and median OS (mOS) was 58 months (95% CI 30.0–86.0). Patients with stage I or II disease had a 5-year OS of 86.7% (mOS not reached), patients with stage III

Table 3 Antineoplastic treatment palliative options and number of therapeutic lines for palliative patients.

Treatment palliative modality	*n* (%)	Number of lines	*n* (%)
Surgical therapy	17 (23.6)	1 line	26 (36.1)
TAE	22 (30.6)	2 lines	26 (36.1)
Other ablative therapies	4 (5.6)	≥ 3 lines	20 (27.8)
PRRT	22 (30.6)		
SSA	49 (68.1)		
Everolimus	11 (15.2)		
Chemotherapy	40 (55.6)		
Radiotherapy	5 (6.9)		

PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogs; TAE, hepatic trans-arterial embolization.
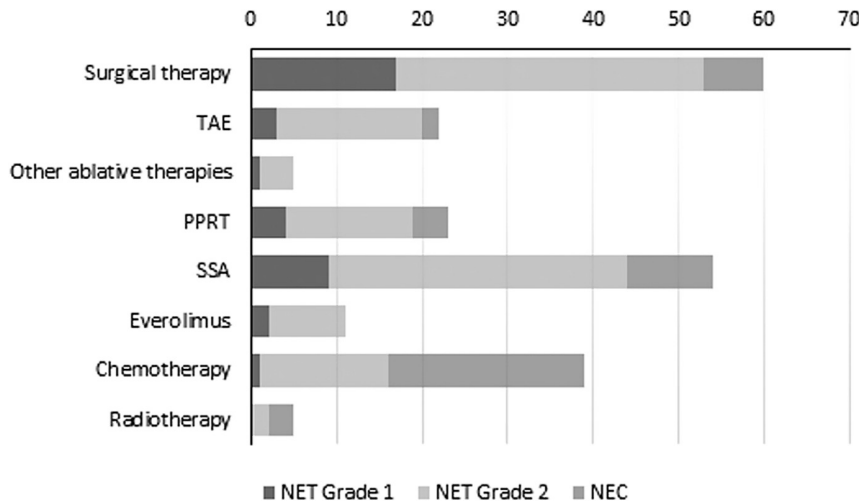
Figure 2
Treatment options according to the WHO 2010
classification. NEC, neuroendocrine carcinoma;
NET, neuroendocrine tumor; PRRT, peptide
receptor radionuclide therapy; SSA, somatostatin
analogs; TAE, hepatic trans-arterial embolization.

disease had a mOS of 47 months (95% CI 18.9–75.1), and patients with stage IV of 29 months (95% CI 18.5–39.5) (Fig. 3). NET grade 1 patients had an mOS of 147 months (95% CI 14.3–279.7), NET grade 2 of 91 months (95% CI 33.5–148.5) months, and NEC patients of 18 months (95% CI 8.7–27.3) (Fig. 4). There were no differences in PFS or OS when comparing different time frame groups: 2006–2011 median PFS was 20 months (95% CI 5.7–34.3) and 2012–2017 median PFS was 26 months (95% CI 18.5–33.5) (HR 0.76, 95% CI 0.47–1.21) (Fig. 5); 2006–2011 mOS was 47 months (95% CI 13.8–80.2) and 2012–2017 mOS was 61 months (95% CI 32.9–89.1) (HR 0.85, 95% CI 0.50–1.47) (Fig. 6). This was also true when comparing according to grade or disease stage between the two-time interval groups (data not shown).

On univariate analysis, the risk of death increased in those patients with NEC (HR 7.64, 95% CI 3.36–16.95), stage III (HR 7.30, 95% CI 2.77–19.23) and IV disease at diagnosis (HR 9.24, 95% CI 4.10–20.80), and primary location of the tumor not in the pancreatic body or tail (HR 2.12, 95% CI 1.23–3.67). No significant association between the risk of death and age (cut-off 60 years), CCI (cut-off 3), symptoms at diagnosis, or diabetes mellitus was found. On multivariate analysis, NEC (HR 2.76, 95% CI 1.17–6.55) and stage III and IV at diagnosis were independent poor prognostic factors (HR 6.02, 95% CI 2.22–16.33 and HR 6.93, 95% CI 2.94–16.32, respectively). Risk of death according to baseline patient and tumor characteristics of PAN-NEN at diagnosis is detailed in Table 4.
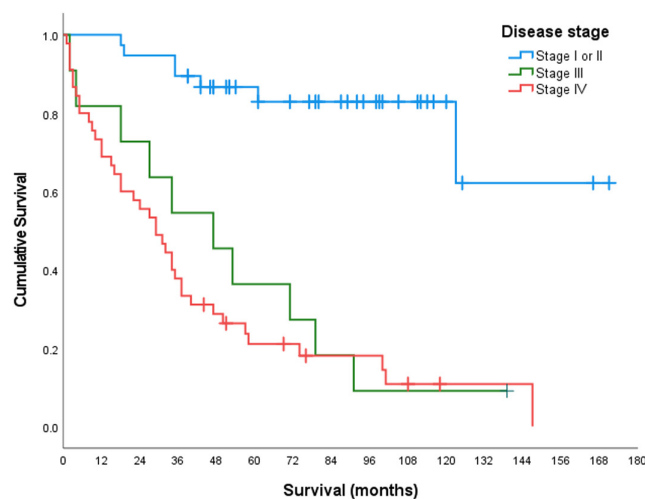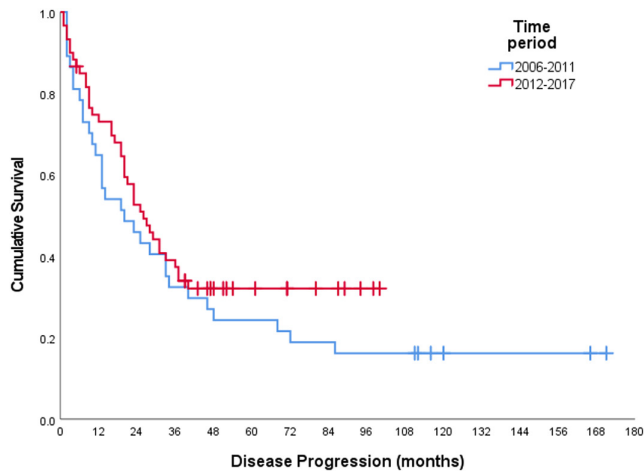

Figure 3
Overall survival of Pan-NEN patients according to disease stage.
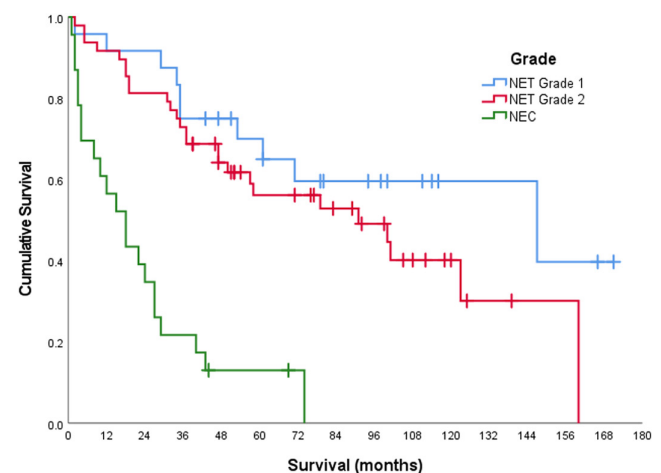
Figure 4
Overall survival of Pan-NEN patients according to WHO 2010 classification. NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
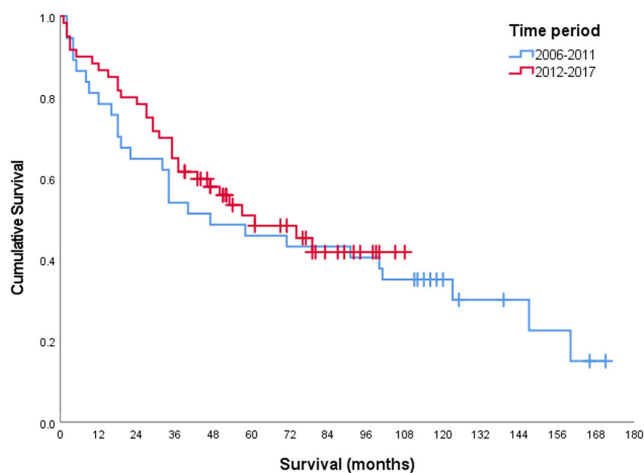
Figure 5
Progression-free survival of Pan-NEN patients after first-line treatment.

Discussion

We performed a retrospective cohort study on patients with Pan-NEN treated and followed in our oncologic center within a 12-year time period.

Median PFS was 25 months and OS was 58 months. Taking into consideration the long follow-up time and the implementation in our center since 2012 of new target therapies such as systemic target therapies and PRRT, we decided to compare patients according to the Pan-NEN date of diagnosis (Yao *et al.* 2011, Faivre *et al.* 2017, Strosberg *et al.* 2017). There were no significant differences in survival outcomes or PFS when comparing the two-time interval groups globally or when considering metastatic disease patients. Additionally, when assessing patients and tumor characteristics and the type of treatment modalities used

Figure 6
Overall survival of Pan-NEN patients according to time period.

Table 4 Risk of death according to baseline patient and tumor characteristics of Pan-NEN at diagnosis.

Characteristic	Multivariate		
	n	HR	95% CI
WHO 2010 classification			
NET grade 1	24	1	
NET grade 2	45	1.06	0.48–2.34
NEC	23	2.76	1.17–6.55
Pancreatic topography			
Body and tail	57	1	
Others	35	1.74	0.90–3.38
Disease stage			
I/II	37	1	
III	10	6.02	2.22–16.33
IV	45	6.93	2.94–16.32

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

between these time periods, no differences were found. This might be due to the indolent course and long survival of the metastatic NET grades 1 and 2, allowing the patients to be submitted to the latest approved therapies. Studies regarding these data are divergent. In one study, median OS of 3.6 years for Pan-NEN was reported in USA SEER database from 2000 to 2012, with improving outcomes on survival in the last years (Dasari *et al.* 2017). In another USA research, there were no relative survival differences between 2000–2010 and 2011–2014 for metastatic Pan-NEN considering the new target therapies approved in 2011 (Kunwor *et al.* 2018).

We noticed a two-fold increase of the Pan-NEN referenced to our center in the most recent years when comparing the two-time intervals (2006–2011 and 2012–2017). This increase may be due to a consolidation of our Institute as a referral center for NEN, or even due to a rise in the incidence of the diagnosis of NEN, as has happened generally around the world (Levi *et al.* 2000, Lepage *et al.* 2004, Hauso *et al.* 2008, Fraenkel *et al.* 2014, Dasari *et al.* 2017).

Considering patients' characteristics, in our study, median patients' age was 60 years and had a small predominance of male gender, in concordance with previous studies (Halfdanarson *et al.* 2008*b*, Yadav *et al.* 2018). In our cohort, CCI was >3 in about half of patients, with almost a third having past or current history of second non-neuroendocrine malignancy and of diabetes mellitus, and more than a third having history of arterial hypertension. Regarding secondary malignancies, a retrospective study of USA SEER database on GEP-NEN found an occurrence of second cancers in 25.8%, though this risk was only associated with gastro-intestinal NEN (Kauffmann *et al.* 2014). One study reported an association

between metabolic syndrome and well-differentiated GEP-NEN, and others reported diabetes mellitus as a possible risk factor for the development of Pan-NEN (Haugvik *et al.* 2015, Leoncini *et al.* 2016, Santos *et al.* 2018, Zhuge *et al.* 2020). Concerning functioning tumors known to be associated with hyperglycemia, we only have five cases – three glucagonoma and two ACTHoma-related Cushing's syndrome. In our study, we found a higher proportion of arterial hypertension and diabetes mellitus in NET grade 2 and of current or past history of non-neuroendocrine malignancy in NET grade 1.

At diagnosis, tumor and hormone secretion-related symptoms were reported in 69.6% and 15.0%, respectively, in accordance with most recent studies, as the incidence of non-functional has been increasing comparatively with functional Pan-NEN (Pape *et al.* 2004, Halfdanarson *et al.* 2008*a*, O'Grady & Conlon 2008).

There were more primary tumors located in pancreas' body and tail, as has been previously demonstrated (Santos *et al.* 2019). Almost half of patients had metastatic disease at presentation and three-quarters had well-differentiated NET grade 1 or 2. We reported a predominance of grade 2 NET, contrary to some studies, where NET grade 1 was typically more frequent (Santos *et al.* 2019, You *et al.* 2019). This might be justified by the type of patients that are referred to our hospital since we are a national reference center: referral of more aggressive tumors, needing highly specialized treatments (institutional referral bias). NET grade 2 and NEC were more often symptomatic at diagnosis, and all secretory NET were grade 2. We also noticed an increase in the frequencies of stage IV disease when comparing NET grade 1, NET grade 2, and NEC.

When assessing therapeutic treatment strategies, they were highly diversified and adapted to disease characteristics, disease stage, tumor and hormone secretion-related symptoms, and patients' characteristics and preferences. According to WHO 2010 classification, therapeutic strategies include several modalities, with surgery being the main treatment for NET grades 1 and 2. SSA, TAE, PRRT, everolimus, and chemotherapy with temozolomide/capecitabine or streptozotocin/5-fluorouracil were used more often in NET grade 2. Chemotherapy was the most frequent option in NEC, mostly a platinum duplet. The high proportion of treatment lines and therapeutic modalities reinforces the need of patients with NEN being referenced to an experienced center with skills in the different therapeutic options available, namely ablative treatments and PRRT. Compared to the previous published national study which included 293 patients from 15 different hospitals, those

treatments were considerably more frequently used at our institution (Santos *et al.* 2019).

Possible prognostic factors associated with increased risk of death, the presence of NEC, stage III and IV disease at diagnosis were associated with a 2.76, 6.02, and 6.93 higher risk, respectively. It is important to notice that some factors that are classically considered with an impact on the risk of death of patients with neuroendocrine neoplasia were not considered in the univariate analysis due to the absence of these data in a significant number of cases. This was true for tumor necrosis, vascular, and perineural invasion, though with an increase on the report of them in the most recent years (Gao *et al.* 2018, Taskin *et al.* 2020).

This study has several limitations as it is a retrospective study, depending largely on the quality of medical registries and of exams availability. For instance, in our cancer institution, electronic medical records were only systematic available since the end of 2012, with some missing information on medical records, namely on patient performance status and disease pathological characteristics. Additionally, this research was conducted between 2006 and 2017, thus WHO 2010 classification was the one applied. For this reason, it is possible that some NEC may correspond to NET grade according to the newest WHO 2017 classification. Future studies, adapted to the WHO 2017 classification of neuroendocrine neoplasms, capable of differentiating NET grade 3 from NEC, would be interesting to assess the outcomes of these neoplasms separately (Tang *et al.* 2016, Pavel *et al.* 2020).

However, the study also has some important strengths. First, the long-time interval for the data collection (12 years) and long follow-up time allow the assessment of the progression and survival outcomes. This is especially important for NET grades 1 and 2 and for localized/locoregional disease, data that most studies (either retrospective or prospective), do not present. Second, though it is an unicenter study, we are the largest national oncologic center for treatment of neuroendocrine neoplasia in Portugal, centralizing a high proportion of NEN diagnosed in the north of the country. Consequently, we have a high level of experience in the treatment of neuroendocrine neoplasms, with the different treatment modalities available for these tumors' management.

In conclusion, pancreatic neuroendocrine neoplasms are a rare heterogeneous group with a diversified therapeutic armamentarium and in which multimodal treatment is frequent, especially for metastatic disease. The impact of new therapeutic options on survival in the real-world is still extensively unexplored. In our study, the new therapeutic approaches did not seem to induce better

survival outcomes. One possible reason for this might be the indolent nature of neuroendocrine tumors grades 1 and 2, with long survival times, allowing patients to be submitted to new target therapies along their disease course. The elaboration of multicentric studies in specialized centers on neuroendocrine neoplasms management would be important for further validation of these results.

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