Original Article

Survival and prognostic factors analysis of 151 intestinal and pancreatic neuroendocrine tumors: a single center experience

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Background: Intestinal and pancreatic neuroendocrine tumors (IP-NETs) are rare tumors with heterogeneous outcomes. The aim of our study was to determine the clinical, therapeutic and pathological factors which impact the overall survival (OS) in IP-NETs.

Methods: All the patients diagnosed with IP-NETs at the Nantes University Hospital between October 1994 and October 2013 were retrospectively analysed. Patients with MEN-1 (Type 1 Multiple Endocrine Neoplasia) or Von Hippel-Lindau syndrome were excluded. Additionally, a prospective analysis of tumor grade (mitotic index and Ki67 index) was performed on tumor samples. OS was evaluated by Kaplan-Meier method and prognostic factors by log-rank test and Cox model.

Results: The study included 151 patients. Median age was 60 (range, 14–81). Primary tumor was pancreatic in 86 patients (56.95%) and intestinal in 65 patients (43.05%). Tumors were metastatic (synchronous or metachronous) in 72 patients (47.7%). The median OS was 157 months. For all IP-NETs, age >65 years (P<0.0001), Ki67 >5% (P=0.03), synchronous metastases (P=0.016), primary tumor size >25 mm (P=0.03) and emergency surgery (P=0.007) were independent poor prognostic factors.

Conclusions: In this large series of patients with IP-NET, age >65 years, Ki67 >5%, primary tumor size >25 mm, synchronous metastases and emergency surgery for acute complications have been identified as independent poor prognostic factors.

Keywords: Neuroendocrine tumors (NETs); pancreatic neuroendocrine tumors; intestinal neuroendocrine tumors; prognostic factors; survival

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Introduction

Neuroendocrine tumors (NETs) are rare tumors, with an incidence of 5 per 100,000 persons per year. Intestinal and pancreatic NETs (IP-NETs) represent about 25% of all NETs (1). As they derive from enterochromaffin cells of the neuroendocrine system, they share some common histological characteristics. However, in terms of hormonal secretion, tumor aggressiveness, local and metastatic evolution, response to treatments and prognosis, NETs form a very heterogeneous group.

Tumor grade, stage, degree of differentiation, and primary tumor size, are well recognized as prognostic factors in NETs. Other factors related to poorer prognosis have been suggested like advanced age at diagnosis, pancreatic tumor localization, the presence of synchronous metastases, and functional character of the tumor, but are still discussed (2-13). Tumor grade, evaluated according to the 2006 ENETS classification based on two proliferative markers [mitotic index (MI) and Ki67 labeling index], is considered the major prognostic factor. According to this classification, tumors are classified in 3 groups: grade 1 tumors: MI <2 and Ki67 ≤2%, grade 2 tumors: MI 2-20 and Ki67 ≥2–20%, and grade 3 tumors: MI >20 and Ki67 ≥20%. Five-year survival of IP-NETs is over 90% for grade 1 tumors, but is lower than 50% for grade 3 tumors. Recently, a new WHO 2017 classification for neuroendocrine pancreatic neoplasms has been introduced, in which two types of grade 3 NETs have been distinguished: (I) well differentiated NETs with Ki67 ≥20%, and (II) poorly differentiated (small or large cell) neuroendocrine carcinomas (14).

The clinical management of NETs is currently guided by different factors related to the patient (age, co-morbidities), and to the tumor (tumor grade, size, degree of tumor differentiation, the presence of synchronous metastases, location of metastases, existence of functional syndrome and tumor resectability). The dynamics of tumor evolution over the time, evaluated by tumor progression after 3 to 6 months, is also taken into account (15,16). Given the relative rarity of these tumors and their great heterogeneity, the therapeutic guidelines for the treatment of IP-NETS remain unclear and are frequently open to clinician judgment. The better knowledge of prognostic factors appears to be essential to help the clinician in the choice of the therapeutic strategy adapted to the aggressiveness of the disease.

The aim of our study was to describe clinical and pathological features determine the clinical, therapeutic and pathological factors which influence the survival in IP-NETs.

Methods

Patients

All the patients diagnosed with well differentiated IP-NETs at the Nantes University Hospital between October 1994 and October 2013, were included. Patients with MEN-1 (Type 1 Multiple Endocrine Neoplasia) and Von Hippel-Lindau syndrome were excluded. The data were collected retrospectively, from medical records, or, if necessary, through the direct telephone contact with the patient or with his family doctor. Moreover, the evaluation of MI and Ki67 index of the tumors was performed prospectively, on tumor samples retrieved prospectively from pathology tissue collection, whenever this information was not available in medical files.

Clinical data and tumor properties

Data regarding first symptoms leading to diagnosis, type of tumor, tumor location, tumor size, presence of metastases at diagnostic or during evolution and metastasis location, were collected.

Histological characteristics

Tumor tissues, of primary tumor or metastases or both when available, were analyzed prospectively by an expert pathologist. MI and Ki67 labeling index were analyzed to determine tumor grade according to the WHO 2010 classification. Ki67, a nuclear marker of cells in active phase of the cell cycle (G1, S1, G2 and mitosis), was analyzed on 2,000 tumor cells in areas of highest nuclear labelling index and expressed as percentage of stained cells. MI was evaluated according to a standard method after hematoxylin and eosin saffron staining, and additionally by using immunostaining with phosphohistone H3 (PPH3)-antibody, which stains the late-G2 and M phases of mitosis. Results were expressed by the number of mitoses per 10 fields. The "global grade" was the highest grade between primary tumor and metastasis.

Statistical analysis

Survival rates were assessed by Kaplan-Meier method. Global survival was determined as the time between obtention of the histological proof of tumor and death from any cause or date of the last news. Differences in median survival were compared using the log-rank test. Cox regression models were used for determination of independent prognostic factors, by univariate analyses. Variables with a P value <0.05 in univariate analysis were included in the multivariate analysis, performed with the Cox proportional hazard model, with a significance level of P<0.05. Analyses were performed using the Graph Pad Prism 6 and XLStat 2017 software.

Ethics

This is a non-interventional study. This study protocol was conform to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and has been approved by the local Ethic Committee of Nantes University Hospital, France. A consent form was not required for this study.

Results

Patients' characteristics and treatments

One hundred and fifty-one patients [82 men (54.3%), median age 60 years (range, 14–81)], were included. Among them, 86 patients (56.95%) had primary pancreatic tumor, and 65 patients (43.05%) had primary intestinal tumor. Fifty-two patients (34.4%) had functional tumors. Seventy-two patients had synchronous or metachronous metastases and from them, 27 (37.5%) had a metastases resection (10 with pancreatic primary tumor and 17 with intestinal primary tumor). One hundred and thirty-nine patients (92.05%) had surgery, either of their primary tumor (n=139) or of their metastases (n=27). If complementary treatment was required, this treatment comprised chemotherapy (n=34), transarterial chemoembolization (n=21), targeted radiotherapy (n=13), somatostatin analogues (n=53), and other treatments (n=16). The mean number of treatment lines was 0.7, median 0 (range, 0–7) (*Table 1*).

Table 1 Patients and tumors characteristics

Characteristic	Total (n=151)	Pancreatic NET, n=86 (56.95%)	Intestinal NET, n=65 (43.05%)
Median age [years (range)]	60 [14–81]	57 [14–81]	66 [31–81]
Men [n (%)]	82 (54.3)	44 (51.2)	38 (53.8)
Functional syndrome [n (%)]	52 (34.4)	31 (36.1)	21 (32.3)
Carcinoid tumor	20 (13.2)	0	20 (30.8)
Insulinoma	21 (13.9)	21 (24.4)	0
Gastrinoma	2 (1.3)	2 (2.3)	0
Glucagonoma	5 (3.3)	5 (5.8)	0
Others[a]	5 (3.3)	4 (4.6)	1 (1.5)
Diagnosis [n (%)]			
Incidental	36 (23.8)	22 (25.6)	14 (21.5)
Functioning syndrome	41 (27.1)	29 (33.7)	12 (18.5)
Others symptoms	71 (47.0)	32 (37.2)	39 (60.0)
Unknown	3 (2.0)	3 (3.5)	0
Date of diagnosis [n (%)]			
Before 2005	71 (47.0)	31 (36.1)	40 (61.5)
2005 and after	80 (53.0)	55 (64.0)	25 (38.5)
Metastatic state [n (%)]			
M1	72 (47.6)	31 (36.1)	41 (63.1)
Synchronous metastases	50 (33.1)	15 (17.4)	35 (53.9)
Metachronous metastases	22 (14.6)	16 (18.6)	6 (9.2)
Metastases locations [n (%)]			
Liver only	29 (19.2)	17 (19.8)	12 (18.5)
Others	43 (28.5)	14 (16.3)	29 (44.6)
Peritoneum	33 (21.8)	9 (10.5)	24 (36.9)
Lungs	8 (5.3)	5 (5.8)	3 (4.6)
Bones	10 (6.6)	3 (3.5)	7 (10.8)

Table 1 *(continued)*

Table 1 *(continued)*

Characteristic	Total (n=151)	Pancreatic NET, n=86 (56.95%)	Intestinal NET, n=65 (43.05%)
Ovaries	6 (4.0)	0	6 (9.2)
Others[b]	10 (6.6)	5 (5.8)	5 (7.7)
Tumor size [n (%)]			
≤25 mm	90 (59.6)	44 (51.2)	46 (70.8)
>25 mm	46 (30.5)	32 (37.2)	14 (21.5)
Unknown	15 (9.9)	10 (11.6)	5 (7.7)
Node state [n (%)]			
N0	7 (4.6)	5 (5.8)	2 (2.3)
N1	60 (39.7)	18 (20.9)	42 (64.6)
Nx	84 (55.6)	63 (73.2)	21 (32.3)
Global grade [n (%)][c]			
G1	57 (37.7)	37 (43)	20 (30.8)
G2	80 (53)	39 (45.3)	41 (63.1)
G3	7 (4.6)	4 (4.6)	3 (4.6)
Unknown	7 (4.6)	6 (7.0)	1 (1.5)
Surgery [n (%)]	139 (92.05)	76 (88.4)	63 (96.9)
Unplanned surgery	20 (13.2)	0	20 (30.8)
Primary tumor resection	139 (92.05)	76 (88.4)	63 (96.9)
Medical treatment [n (%)]			
Chemotherapy[d]	34 (22.5)	22 (25.6)	12 (18.5)
Transarterial chemoembolization	21 (–13.9)	5 (5.8)	16 (24.6)
Targeted radiotherapy	13 (8.6)	6 (7)	7 (10.8)
Somatuline analogues	53 (35.1)	16 (18.6)	37 (56.9)
Others[e]	16 (10.6)	13 (15.1)	3 (4.6)

[a], somatostatinoma, somatoliberoma, VIPoma, Ppoma; [b], others: spleen, brain or colon metastases; [c], according to the WHO classification; [d], including targeted therapies; [e], external beam radiation therapy, radiofrequency ablation, alpha interferon. NET, neuroendocrine tumor.

All IP-NETs

In univariate analysis, the median overall survival (OS) was 157 months. Age >65 years (HR =3.46; 95% CI, 2.45–7.61; P<0.0001), I-NET (HR =2.16; 95% CI, 1.30–3.70; P=0.0035), synchronous metastases (HR =2.61; 95% CI, 1.71–5.43; P=0.0002), ovarian metastasis (HR =2.68; 95% CI, 1.21–20.46; P=0.03), and emergency surgery (HR =2.77; 95% CI, 1.89–10.95; P=0.0008), were identified as statistically significant poor prognostic factors. A Ki67 >5% had a negative impact on survival (HR =2.77; 95% CI, 1.89–4.09; P=0.006), whereas no statistically significant impact was found for a Ki67 ≥2%.

In multivariate analysis, age >65 years old (HR =3.87; 95% CI, 2.19–6.83; P<0.0001), Ki67 >5% (HR =2.43; 95% CI, 1.08–5.46; P=0.03), synchronous metastases (HR =2.37; 95% CI, 1.17–4.76; P=0.016), primary tumor size >25 mm (HR =1.96; 95% CI, 1.08–3.54; P=0.03) and emergency surgery (HR =2.64; 95% CI, 1.30–5.36; P=0.007) were independent poor prognostic factors (*Table 2*).

Non-metastatic pancreatic NETs (n=71)

In univariate analysis, OS was higher for insulinomas as compared to other tumors [HR =0.19; 95% CI, 0.11–1.12; P=0.08). Ki67 >5% (HR =3.43; 95% CI, 1.41–14.57; P=0.013), and age >65 years (HR =8.88; 95% CI, 3.93–39.36; P<0.0001), were poor prognostic factors.

In multivariate analysis, age >65 years (HR =13.62; 95% CI, 2.99–62.04; P=0.001) and Ki67 >5% (HR =4.88; 95% CI, 1.58–15.02; P=0.006) were the only independent poor prognostic factors (*Table 3*).

Table 2 Prognostic factors for overall survival in all neuroendocrine tumors

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (>65 years old)	3.46 (2.45–7.61)	<0.0001	3.87 (2.19–6.83)	<0.0001
Intestinal NETs	2.16 (1.30–3.70)	0.0035	1.20 (0.58–2.51)	0.62
Tumor size (>25 mm)	1.38 (0.80–2.48)	0.24	1.96 (1.08–3.54)	0.03
Synchronous metastasis	2.61 (1.71–5.43)	0.0002	2.37 (1.17–4.76)	0.016
Ovarian metastasis	2.68 (1.21–20.46)	0.03	1.57 (0.58–4.26)	0.37
Global tumor grade G2/G3	1.57 (0.89–2.63)	0.12	0.56 (0.23–1.41)	0.22
Ki67				
>2%	1.47 (0.86–2.48)	0.16	–	–
>5%	2.77 (1.89–4.09)	0.006	2.43 (1.08–5.46)	0.03
MI				
≥2	0.74 (0.41–1.30)	0.28	–	–
≥5	0.63 (0.26–1.30)	0.13	–	–
Emergency surgery	2.77 (1.89–10.95)	0.0008	2.64 (1.30–5.36)	0.007

NET, neuroendocrine tumor; CI, confidence interval; MI, mitotic index; HR, hazard ratio.

Table 3 Prognostic factors for non-metastatic pancreatic NETs (n=71)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Tumor secretion insulinomas	0.19 (0.11–1.12)	0.08	–	–
Tumor size				
≥20 mm	0.65 (0.19–2.08)	0.48	–	–
Global tumor grade G2/G3	2.62 (0.89–7.28)	0.08	–	–
Ki67				
>2%	2.89 (0.98–8.49)	0.05	–	–
>5%	3.43 (1.41–14.57)	0.013	4.88 (1.58–15.02)	0.006
MI				
≥2	0.75 (0.21–2.57)	0.63	–	–
≥5	0.72 (0.12–3.73)	0.66	–	–
Age (>65 years old)	8.88 (3.93–39.36)	<0.0001	13.62 (2.99–62.04)	0.001

NET, neuroendocrine tumor; CI, confidence interval; MI, mitotic index; HR, hazard ratio.

Pancreatic NET's with synchronous metastases (n=15)

In univariate analysis, age >60 years and OMS score ≥2 were significant poor prognostic factors, but only borderline significant in multivariate analysis with HR =6.09 (95% CI, 0.92–40.50; P=0.06) and HR =5.47 (95% CI, 0.99–30.34; P=0.052), respectively (*Table 4*).

Non metastatic intestinal NET (n=30)

In univariate analysis, age >65 years (HR =5.22; 95% CI, 1.71–14.40; P=0.004) and unplanned surgery (HR =3.30; 95% CI, 1.18–12.04; P=0.02) were poor prognostic factor.

In multivariate analysis, only age >65 years old (HR =5.37; 95% CI, 1.49–19.41; P=0.01) was an independent prognostic factor (*Table 5*).

Intestinal NET with synchronous metastases (n=35)

In univariate analysis, age >65 years old (HR =2.73; 95% CI, 1.31–8.10; P=0.01), ovarian metastases (HR =2.59; 95% CI, 1.08–17.12; P=0.04), Ki67 >5% (HR =3.27; 95% CI, 1.32–8.83; P=0.012) and unplanned surgery (HR =2.39;

Table 4 Prognostic factors for overall survival in pancreatic NETs with synchronous metastases (n=15)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Ki67				
>2%	1.18 (0.15–9.02)	0.88	–	–
>5%	0.54 (0.11–2.65)	0.46	–	–
MI				
≥2	0.26 (0.01–1.41)	0.10	–	–
≥5	0.71 (0.06–7.50)	0.75	–	–
Surgery of primary tumor	1.13 (0.13–10.48)	0.90	–	–
Age >60 years old	4.1 (1.47–93.83)	0.03	6.09 (0.92–40.50)	0.06
Chemotherapy	0.13 (0.015–1.07)	0.06	–	–
OMS ≥2	3.89 (1.21–71.17)	0.04	5.47 (0.99–30.34)	0.052

NET, neuroendocrine tumor; CI, confidence interval; MI, mitotic index; HR, hazard ratio.

95% CI, 1.07–5.34; P=0.034) were poor prognostic factors.

In multivariate analysis, no significant independent prognostic factor was identified (*Table 6*).

Discussion

In the present study, we analysed the data from 151 patients with IP-NETs, diagnosed and treated in a single center. As IP-NETs are rare and frequently have slow progression, the data were collected retrospectively from 1994 until 2013. We report a large cohort, with a long follow-up. The median survival time for all patients was 161 months. Demographic characteristics and prognostic factors of survival identified in our study are in accordance with those previously reported. In univariate analysis, P-NETs had a better prognosis than I-NETs. In the literature, tumor primary site has been proved to affect OS, with a better outcome for I-NETS (5,17-19). The different outcome observed in our study may be in part related to the high proportion of insulinomas, known for a better prognosis, included in our study (24% of P-NETs), and to a selection bias in a tertiary center expert in pancreatic surgery. In multivariate analysis, for all IP-NETs, the age superior to 65 years, Ki67 proliferation index superior to 5%, the primary tumor size superior to 25 mm, the presence of synchronous metastases and emergency surgery for acute complications, were significant independent poor prognostic factors.

Age at diagnosis appears to be a strong prognostic factor, as previously reported (17,20,21). It could be explained in part by patients' comorbidities and deaths from other causes than the tumor. However, in patients older than 75 years old, none received more than 1 line of treatment for their IP-NET. Elderly patients may be undertreated, and it could have a significant impact on survival.

Tumor grade, according to the WHO classification, is an established strong prognostic factor (14). In our study, tumor grade was confirmed in a prospective manner, after a systematic analysis of tumor tissue to determine the Ki67, even for NETs diagnosed before 2005. Tumor grade depends on mitotic counts and Ki67. Those 2 proliferative markers are continuous values, but cuts off of 2 and 20 are used to grade the tumor in current guidelines (15,22). In clinical practice, grade 2 NETs form a very heterogeneous group and survival in this group can be very different between a "low" grade 2 with a Ki67 close to 2% or a "high" grade 2 with a Ki67 close to 20%. In our study, a cut off of 5% turned out to be more relevant than a cut off of 2% for Ki67, which has already been suggested (3,6,23). The WHO classification of NET should therefore probably be revised. There are several biomarkers and genetic markers currently under study which can become prognostic markers in the future, but cannot be recommended in clinical practice yet (24-26).

For I-NETs, the resection of primary tumor is generally advocated (ESMO and ENETS guidelines) (27,28). The absence of primary tumor resection can lead to acute

Table 5 Prognostic factors for overall survival in non-metastatic intestinal neuroendocrine tumors (n=30)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (>65 years old)	5.22 (1.71–14.40)	0.004	5.37 (1.49–19.41)	0.01
Unplanned surgery	3.30 (1.18–12.04)	0.02	2.62 (0.93–7.42)	0.07
Ki67				
>2%	0.13 (0.09–0.83)	0.13	–	–
>5%	0.42 (0.12–2.21)	0.38	–	–
Medical therapy				
Somatostatin analogs	0.2 (0.11–1.13)	0.08	–	–

NET, neuroendocrine tumor; CI, confidence interval; MI, mitotic index; HR, hazard ratio.

Table 6 Prognostic factors for overall survival in intestinal NETs with synchronous metastases (n=35)

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (>65 years old)	2.73 (1.31–8.10)	0.01	2.24 (0.86–5.79)	0.09
Ovarian metastasis	2.59 (1.08–17.12)	0.04	2.84 (0.93–8.72)	0.068
Size ≥25 mm	3.06 (1.64–14.05)	0.006	0.56 (0.23–1.41)	0.22
Ki67				
>2%	2.34 (0.65–5.88)	0.24	–	–
>5%	3.27 (1.32–8.83)	0.012	2.49 (0.88–7.03)	0.08
Unplanned surgery	2.39 (1.07–5.34)	0.034	2.71 (0.81–9.1)	0.11
Medical therapy				
Somatostatin analogs	0.78 (0.15–3.79)	0.73	–	–
Chemotherapy	1.23 (0.50–3.09)	0.64	–	–

NET, neuroendocrine tumor; CI, confidence interval; HR, hazard ratio.

complications, such as digestive occlusion, perforation or intestinal ischemia requiring emergency surgery, which impacts the OS. Primary tumors should be resected early to avoid acute complications. In the subgroup of metastatic pancreatic NET in our study, the benefits of primary tumor resection could not be demonstrated, may be due to the small sample size of this population. In other retrospective studies, the surgical resection of the primary tumor in metastatic P-NET was associated with better cancer-specific and OS (29,30). Primary tumor resection could also enhance the response to further treatments, such a peptide receptor radionuclide therapy (PRRT), and improve progression free survival (31).

The survival benefits of the surgical resection of metastases are still controversial (32-36). In our study, there was no impact on survival of surgical resection of metastasis, for all NETS, as well as in P-NETs and I-NETs subgroups. No impact on OS of chemotherapies and targeted therapies were found. But the follow-up since 2007 and the beginning of use of modern chemotherapies and targeted therapies is probably not long enough to find a significant effect on global survival and 5-year survival for these indolent

tumors.

There are several limitations to our study. This is a retrospective study, with patients including over a long period. Thus, all the patients could not have been treated with the most recent therapies, targeted therapies or PRRT, which can impact OS. All the NET subgroups were not equally represented, as most of the patients were referred for the resection of P-NETs. Other factors such as comorbidities, smoking and alcohol consumption, and laboratory results could not be documented in our study. However, tumor tissue was analysed prospectively by an expert pathologist.

In conclusion, despite these limitations, we report a large series of patients with IP-NET treated in a single center and identify strong prognostic factors that could help to define therapeutic strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This is a non-interventional study. This study protocol was conform to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and has been approved by the local Ethic Committee of Nantes University Hospital, France. A consent form was not required for this study.

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