

# Prognosis after curative resection of non-metastatic pancreatic neuroendocrine tumors: a retrospective tertiary center study

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## Abstract

**Background** Pancreatic neuroendocrine tumors (pNETs) are rare tumors with heterogeneous outcomes. The aim of our study was to determine the long-term outcome, recurrence patterns, as well as the clinical and pathological factors that impact time-to-recurrence (TTR), recurrence-free survival (RFS), and overall survival (OS) in pNETs treated with curative surgery.

**Methods** Data for all patients who underwent radical surgery with curative intent for non-metastatic pNETs were obtained from a prospectively maintained database of the University Hospitals Leuven. Data from September 2002 until November 2021 were analyzed retrospectively. Patients with metastatic disease and/or neuro-endocrine carcinoma were excluded. Median follow-up time was calculated using the reverse Kaplan-Meier method. A Cox proportional hazards model was used to assess variables associated with recurrence.

**Results** The study included 128 patients. Only 8 patients (6.3%) had recurrent disease over a median follow up of 44.4 months (interquartile range [IQR] 29.8-74.7). The median TTR was 38.7 months (IQR 18.0-46.2). Univariate analysis showed that multiple endocrine neoplasia type 1 (MEN-1) and R1-status were statistically significant predictors for disease recurrence.

**Conclusions** In our series of patients treated with surgery for non-metastatic, well-differentiated pNETs, recurrence was low at 6.3%. MEN-1 and R1-status were predictors for recurrence in univariate analysis.

**Keywords** Neuroendocrine tumors, pancreatic neuroendocrine tumors, surgery, prognostic factors

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## Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that arise from neuroendocrine cells throughout the body and are able to produce peptides that cause characteristic hormonal syndromes [1,2]. About two thirds of NETs arise in the gastroenteropancreatic system (GEP-NETs), and of these 20% are pancreatic NETs (pNETs) [3]. About 30-40% of all pNETs are called functional and are able to produce peptides, which may result in different clinical syndromes: e.g., insulinoma, Zollinger-Ellison, Verner-Morrison, glucagonoma, somatostatinomas, ectopic adrenocorticotrophic hormone- and parathyroid hormone-related peptide syndromes [4]. The incidence and distribution pattern of NETs show global differences [5]. However, there has been an increasing incidence worldwide over the last decades, mostly due to the increased use of radiographic imaging [2,6,7]. As a consequence, there is an increase in surgical resections for NETs, with pancreatic NETs (pNETs) being the second

most frequent reason for pancreatic surgical resection after pancreatic adenocarcinoma [7,8], the latter accounting for 93% of pancreatic cancers [9]. Although radical surgery is regarded as the only curative treatment [10], the benefits of surgery must be weighed against the perioperative morbidity and mortality [11]. In addition, scientific evidence suggests that small, non-functional, well-differentiated pNETs could be managed non-operatively when they are minimal or when no growth is observed after serial imaging [12]. The 2016 European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines also advocate a conservative approach in non-metastatic, non-functional tumors  $\leq 2$  cm [13]. However, when curative resection is performed, it remains difficult to predict recurrence, which has led to debate about follow-up strategies for this heterogeneous group of tumors [10,14,15]. Over the past decades, several studies have tried to provide an answer to this question by establishing prognostic scoring systems and nomograms to predict recurrence [1,16,17]. In our series we aimed to determine long-term outcomes and recurrence patterns, as well as the clinical and pathological factors that impact recurrence and overall survival (OS) in well-differentiated non-metastatic pNETs treated with curative surgery.

## Patients and methods

### Study population

A retrospective study was performed using a preexisting prospectively-collected database that included patients with neuroendocrine neoplasms (NEN) admitted to our tertiary Digestive Oncology unit of the University Hospitals Leuven and underwent surgical resection with curative intent for non-metastatic pNETs. Following approval from the Research Ethics Committee UZ/KU Leuven (MP017750), the medical records of patients diagnosed with pNETs who were included in the pre-existing NEN-database were analyzed retrospectively. All patients who had well-differentiated G1-G3 pNETs, as defined by the 2017 World Health Organisation (WHO) Classification [18], and underwent radical surgery with curative intent were considered for inclusion. Patients with distant metastases and/or neuroendocrine carcinoma (NEC) were excluded. In the preexisting database, 128 patients were eligible for inclusion and underwent surgery between September 17, 2002, and November 22, 2021.

### Data collection

Variables were retrospectively collected from our electronic health records system and anonymously transferred to a common database. We collected the following clinical data: demographics (age, sex), functional syndrome upon diagnosis, hereditary syndromes, type of surgery, tumor characteristics (size and staging of primary pNET), and pathological features:

differentiation status (G1-3), Ki-67 index, resection margin status (R-status), lymph node involvement, lymphovascular invasion (LVI), vascular invasion (VI) and perineural invasion (PNI). Patients' follow-up information (date, site of recurrence and survival data) were collected to calculate OS, recurrence-free survival (RFS), and time-to-recurrence (TTR). OS was defined as the time from the date of primary surgery until the date of death from any cause. RFS was defined as the time from the date of primary surgery until the date of radiologic recurrence or death. TTR was defined as the time from date of primary surgery until the time of recurrence. Patients without recurrence were censored at the last oncological follow up. The TNM stage was determined based on the ENETS TNM classification (2010) [19], while tumor grade was determined by the 2017 WHO Classification [18].

### Statistical analysis

Data were reported as mean  $\pm$  standard deviation when normally distributed and as median with interquartile range when not normally distributed. Categorical variables were reported as counts and percentage. Normality of data was assessed using the Shapiro-Wilk test. Time to last follow up was calculated using the reverse Kaplan-Meier method. A Cox proportional hazards model was used to assess variables associated with recurrence. A 2-sided P-value  $\leq 0.05$  was considered statistically significant. Coefficients from the Cox models were reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Statistical analyses were performed using the R-software environment (Version 4.0.3). There was no correction applied for multiple comparisons, in view of the relative low number of patients implying a high chance of type II errors.

## Results

### Characteristics of the full cohort of patients

In total 128 patients were included. Baseline characteristics of the full cohort are listed in Table 1. The mean age at diagnosis was  $57.0 \pm 14.0$  years; 51.6% were male and 49.4% female. In our analysis, 11.7% of the population suffered from a functional syndrome, with insulinoma (10.9%) being the most frequently reported. In addition, 8.7% of the cases were attributable to a hereditary syndrome: 8 cases of multiple endocrine neoplasia type I (MEN-1), 2 cases of von Hippel-Lindau and 1 case of Li-Fraumeni syndrome. The median follow up after surgical resection was 44.4 months (29.8-74.7). Most of the patients presented with ENETS stage I disease (48.8%), with low-grade histological features (G1: 58.3%). Seven patients (5.5%) had an R1-resection. Eight patients (6.3%) had recurrent disease. All-cause mortality was 3.9%; however, none of the deaths were attributable to the underlying NET. The 1-year OS was 98.4% (no. at risk 121, 95%CI 0.96-1.00) and the 3-year OS was 97.5% (no. at risk 85, 95%CI 0.95-1.00).

**Table 1** Baseline characteristics of (a) the full cohort (n=128), (b) the recurrence cohort (n=8) and (c) the non-recurrence cohort (n=120)

Characteristics	All patients (n=128)	(a)	Recurrence (n=8)	(b)	No recurrence (n=120)	(c)
Sex	66 (51.6%) Male 62 (49.4%) Female	/128	2 (25.0%) Male 6 (75.0%) Female	/8	64 (53.3%) Male 6 (46.7%) Female	/120
Age	56.9±13.9	/128	59.3±12.0	/8	56.7±14.0	/120
Functional syndrome	15 (11.7%) Insulinoma: 14 (10.9%) Glucagonoma: 1 (0.1%)	/128	0	/8	15 (12.5%) Insulinoma: 14 (10.9%) Glucagonoma: 1 (0.1%)	/120
Hereditary syndrome	11 (8.7%) MEN-1: 8 (6.3%) von Hippel-Lindau: 2 (15.7%) Li-Fraumeni: 1 (0.8%)	/127	3 (37.5%) MEN-1: 3 (37.5%)	/8	8 (6.7%) MEN-1: 5 (0.04%) von Hippel-Lindau: 2 (0.01%) Li-Fraumeni: 1 (0.01%)	/119
Grade (Ki-index)	G1 (<2) 74 (58.3%) G2 (2-20) 53 (41.7%) G3 (>20) 6 (4.7%)	/127	3 (37.5%) 5 (62.5%) 0 (0.0%)	/8	71 (59.7%) 42 (35.3%) 6 (5.0%)	/119
Differentiation	Well differentiated: 128 (100%)	/128	Well differentiated: 8 (100%)	/8	Well differentiated: 120 (100%)	/120
ENETS TNM	T1N0: 60 (48.4%) T1N1: 2 (1.6%) T2N0: 36 (29.0%) T2N1: 6 (4.8%) T3N0: 9 (7.3%) T3N1: 8 (6.5%) T4N0: 1 (0.8%) T4N1: 2 (1.6%)	/124	T1N0: 1 (12.5%) - T2N0: 4 (50.0%) T2N1: 1 (12.5%) T3N0: 1 (12.5%) T3N1: 1 (12.5%) - -	/8	T1N0: 59 (50.9%) T1N1: 2 (1.7%) T2N0: 32 (27.6%) T2N1: 5 (4.3%) T3N0: 8 (6.9%) T3N1: 7 (6.0%) T4N0: 1 (0.9%) T4N1: 2 (1.7%)	/116
ENETS Stage	I: 60 (48.8%) IIA: 36 (29.3%) IIB: 10 (8.1%) IIIA: - IIIB: 16 (13.0%) IV: 1 (8.1%)	/123	I: 1 (12.5%) IIA: 4 (50.0%) IIB: 1 (12.5%) - IIIB: 2 -	/8	I: 59 (51.3%) IIA: 32 (27.8%) IIB: 9 (7.8%) - IIIB: 14 (12.2%) IV: 1 (0.9%)	/115
Size (mm)	20.0 (12.0-30.0)	/125	32.3±11.9	/8	19.0 (12.0-30.0)	/117
Lymph node	19 (15.8%)	/120	2 (28.6%)	/7	17 (15.0%)	/113
LVI	25 (22.1%)	/113	3 (42.9%)	/7	25 (20.8%)	/106
VI	4 (3.5%)	/115	0 (0.0%)	/7	4 (3.7%)	/108
PNI	16 (14.4%)	/111	1 (14.3%)	/7	14 (13.5%)	/104
Surgery type	Whipple :36 (28.1%) Central pancreatectomy: 13 (10.2%) Distal pancreatectomy: 30 (23.4%) Distal pancreatectomy+splenectomy: 34 (26.6%) Enucleation: 14 (10.9%) Distal pancreatectomy+multivisceral excision: 1 (0.01%)	/128	Whipple: 2 (25.0%) Central pancreatectomy: 1 (12.5%) Distal pancreatectomy: 1 (12.5%) Distal pancreatectomy+splenectomy: 4 (50.0%) - - -	/8	Whipple: 34 (28.3%) Central pancreatectomy: 12 (10.0%) Distal pancreatectomy: 29 (24.2%) Distal pancreatectomy+splenectomy: 30 (25.0%) Enucleation: 14 (11.7%) Distal pancreatectomy+multivisceral excision: 1 (0.01%)	/120
R1 resection	7 (5.5%)	/127	2 (25.0%)	/8	5 (4.2%)	/119
Invasion adjacent organs	3 (2.4%)	/127	0 (0.0%)	/8	3 (2.5%)	/119
Recurrence Time surgery-recurrence (months)	8 (6.3%)	/127	8 (100%) Locoregional: 6 (75.0%) Liver: 3 (37.5%) 38.7 (18.0-46.2)	/8		/8

(Contd...)

Table 1 (Continued)

Characteristics	All patients (n=128)	(a)	Recurrence (n=8)	(b)	No recurrence (n=120)	(c)
Death	5 (3.9%)	/127	0 (0.0%)	/8	5 (0.04%)	/119
Cause of death	Unknown: 1 (20.0%) Cardiac arrest: 1 (20.0%) Abdominal sepsis: 1 (20.0%) Lymphoma: 1 (20.0%) Pancreatic adenocarcinoma: 1 (20.0%)	/5	-	-	Unknown: 1 (20.0%) Cardiac arrest: 1 (20.0%) Abdominal sepsis: 1 (20.0%) Lymphoma: 1 (20.0%) Pancreatic adenocarcinoma: 1 (20.0%)	/5
Time to last FU (months)	44.4 (29.8-74.7)	/127	-	-	52.7 (31.7-78.6)	/119

LVI, lymphovascular invasion; VI, vascular invasion; PNI, perineural invasion; FU, follow up; ENETS, European Neuroendocrine Tumor Society

### Characteristics of the cohort with disease recurrence vs. no recurrence

Only 8 patients (6.3%) had recurrent disease. In the recurrence-group, the median TTR was 38.7 months (18.0-46.2). The Kaplan-Meier curve for TTR for all 128 patients is illustrated in Fig. 1. The 1-year RFS was 97.6% (no. at risk 121, 95%CI 0.95-1.00) and the 3-year RFS was 93.9% (no. at risk 85, 95%CI 0.90-0.98). Compared to the non-recurrence cohort, patients with recurrent disease had a numerically higher stage of disease (only 12.5% had ENETS stage I disease in the recurrence cohort versus 51.3% in the non-recurrence cohort,  $P=0.08$ ) and higher histological grading (62.5% G2-3 in the recurrence cohort vs. 40.7% G2-3 in the non-recurrence cohort,  $P=0.40$ ).

Patients with recurrence presented with locoregional recurrence and/or liver metastasis. Compared to the other patients, all patients with MEN-1 were significantly younger, with a median age of  $39.1 \pm 18.0$  vs.  $58.1 \pm 12.8$  years ( $P < 0.001$ ). The recurrence pattern of all MEN-1 patients with recurrent disease ( $n=3$ ) was locoregional in the remnant pancreas. Patients with hereditary syndromes other than MEN-1 did not have recurrent disease.

### Univariate analysis

According to the univariate analysis, only MEN-1 ( $P=0.0047$ ) and R1-status ( $P=0.0415$ ) were statistically significant predictors for recurrent disease (Table 2, Supplementary Table 1).

### Discussion

pNETs are rare, with heterogeneous tumors accounting for 2-5% of pancreatic tumors [6,7]. Among the different anatomic sites of NETs, pNETs are known to have the worst prognosis [20], with an estimated 5-year OS rate of about 80% for localized disease and 30% for metastatic disease [21]. Although radical surgery is regarded as the only curative treatment [10], predicting recurrence after curative

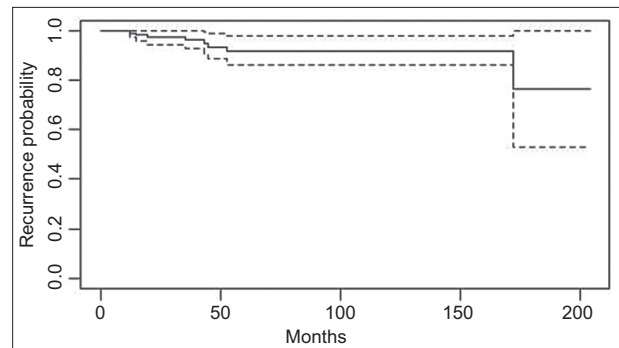


Figure 1 Kaplan-Meier curve for time to recurrence for all 128 patients. The black dotted lines depict the 95% confidence interval

resection for this heterogeneous group of tumors is still a matter of debate [1,16,17], leading to questionable follow-up strategies [10,15]. In our study we aimed to determine recurrence patterns, long-term outcomes, as well as clinical and pathological factors that impact recurrence in well-differentiated non-metastatic pNETs treated with curative surgery.

Our study provided detailed and instructive demographic, clinical and pathological data from a cohort of patients treated at a high-volume tertiary ENETS center of excellence. The mean age at diagnosis in our study population was  $57.0 \pm 14.0$  years, which is in accordance with earlier demographic data [2,22]. In line with other reports, 11.7% of patients presented with a functional syndrome upon diagnosis, with insulinoma being the most frequently reported [8,22]. Given the median follow-up of 44.4 months, reliable long-term results could be calculated.

Although earlier studies have reported recurrence rates ranging from 12.3-42.0% following surgical resection [22-25], only 6.3% of our cohort suffered disease recurrence, with a 3-year RFS of 93.9% (no. at risk 85, 95%CI 0.895-0.984). The median TTR was calculated as 38.7 months (95%CI 18.0-46.2). The overall mortality rate within the entire cohort stood at 3.9%, and more interestingly, none of these deaths were attributable to the underlying NET. The lower recurrence and mortality rate of our cohort could be explained by the fact that we used data from a uniform cohort of well-differentiated, non-metastatic pNETs, whereas earlier reports used a more heterogeneous

**Table 2** Statistically significant risk factors for recurrence after univariate analysis using a Cox proportional hazards model

Variable	Recurrence (n=8)	No recurrence (n=120)	Univariate analysis HR (95%CI)	P-value
MEN 1	3 (37.5%)	5 (0.04%)	8.2 (1.9-35.4)	0.0047
R1 resection	2 (25%)	5 (4.2%)	5.6 (1.1-29.2)	0.0415

HR, hazard ratio; CI, confidence interval

study population, including patients with NECs and/or patients who underwent curative metastasectomy, which are assumed to have a more aggressive disease behavior [22-26]. Since we know that higher histopathological grades and Ki-67 index [1,5,8,16,27], as well as tumor size [1,8,16,28-30], are associated with a higher risk of recurrence and shorter overall survival, it is in line with our expectations that our well-defined cohort of well-differentiated pNETs would have a better prognosis. Additionally, the majority of tumors within our cohort were small and predominantly categorized as ENETS stage 1 disease, with a higher numerical prevalence of G1 tumors.

All taken together, the low recurrence rate (6.3%) of our cohort suggests that curatively resected well-differentiated, non-metastatic pNETs have a very good prognosis. One pertinent question to consider is whether the impressive survival rates are attributable to surgical resection, or whether they merely signify a proof of concept that small pNETs (<2 cm) exhibit a non-aggressive disease behavior and thus could be viable candidates for a watchful waiting approach, as suggested by the 2016 ENETS guidelines [13]. For example, a recent prospective cohort study (PANDORA), examining a watchful waiting strategy for non-functional pNETs (<2 cm), revealed that only a small fraction of patients experienced tumor progression, indicating that short-term monitoring with a watchful waiting strategy is both safe and feasible [31]. Apart from this, there are emerging, alternative non-surgical options such as endoscopic ultrasound-guided ablative techniques that may be a possible alternative for surgically unfit patients [32].

Univariate analysis of our data showed that MEN-1 syndrome and R1-status were the only statistically significant predictors for recurrent disease. The predictive value of R1-status seems to be evident, since oncological curative surgery aims to achieve negative resection margins (R0). Nevertheless, residual tumor infiltration on margins (R1) is described in 6-15% of pancreatic NET resections [8]. In our study population, only 7 patients (5.5%) had a R1-resection. The predictive value of MEN-1 for disease recurrence seems logical, since pNETs arise in 30-80% of patients with MEN-1, mostly presenting as multiple pancreatic microadenomas that tend to recur frequently [33,34]. The patients with MEN-1 who developed recurrence in our cohort had locoregional recurrence in the remnant pancreas. This might raise the question whether this is an expected manifestation of the biological behavior of MEN-1, rather than "true recurrence". Next to MEN-1, we know that NETs can arise in other complex hereditary endocrine disorders such as familial paragangliomatosis, neurofibromatosis type 1, von Hippel-Lindau disease and tuberous sclerosis [35]. Patients with

hereditary syndromes other than MEN-1 did not have disease recurrence in our cohort. However, given the rarity of these syndromes and the small number of these specific patients in our cohort, it is difficult to draw strong conclusions.

We are aware of the fact that the limited sample size and low recurrence rate could explain why we were unable to find statistically significant clinicopathological factors associated with disease recurrence. For instance, a recent systematic review by Broadbent *et al* including 63 studies with a total of 13,715 patients with gastroenteropancreatic NETs, concluded that the following factors predicted worse RFS after multivariate analysis: vascular resection, resection of metastatic disease, G2-3 disease, tumor size >20 mm, R1 resection, LVI and PNI, Ki-67 >5%, and any lymph node positivity [28]. Similarly, Li *et al* conducted a concise meta-analysis, including 2863 patients to research prognostic factors for recurrence of resected well-differentiated pNETs, and concluded that G2 disease, lymph node invasion, surgical resection margin, VI and PNI could be predictive for recurrence [30].

Limitations of our study are the size of our cohort and the low recurrence rate, making it difficult to find statistically significant predictors for recurrence, since our results might be underpowered. Although we used a prospectively maintained database, most of the data were collected and analyzed retrospectively. As a consequence, it is difficult to draw strong and definitive conclusions. Nevertheless, we were able to unravel the long-term prognosis of well-differentiated, non-metastatic pNETs treated by curative surgery at an ENETS center of excellence. However, larger multicenter prospective studies will be necessary to create a better understanding of the biological behavior and recurrence pattern of well-differentiated non-metastatic pNETs treated with curative surgery.

In conclusion, in this retrospective analysis of 128 patients who underwent curative resection for well-differentiated non-metastatic pNETs, only 6.3% of patients had recurrent disease. MEN-1 and R1-status were found to be statistically significant predictors of recurrence in univariate analysis. These results suggest that curatively resected (R0-status achieved) well-differentiated pNETs without underlying hereditary syndromes have a very good prognosis.

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### Summary Box

#### What is already known:

- Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of tumors with variable outcomes
- Different studies have tried to establish risk factors for recurrence after curative resection; however, it remains difficult to predict recurrence, which has led to debate about follow-up strategies

#### What the new findings are:

- In this retrospective study we aimed to evaluate the long-term results, recurrence patterns, as well as the clinical and pathological factors that impact prognosis and overall survival in pNETs treated with curative surgery
- In this series 128 patients underwent curative resection for a well-differentiated, non-metastatic pNET and the recurrence rate stood at 6.3%; none of the deaths were attributable to the underlying NET
- Multiple endocrine neoplasia type 1 and R1-status were found to be predictors for recurrence in univariate analysis
- These results suggest a very good prognosis for this specific group of patients

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## Supplementary material

**Supplementary Table 1** Supplementary table of *P* values of non-significant variables after univariate analysis

Variable	Recurrence (n=8)	No recurrence (n=120)	Univariate analysis HR (95% CI)	P-value
Sex	2 (25.0%) Male 6 (75.0%) Female	64 (53.3%) Male 6 (46.7%) Female	3.7 (0.7-18.6)	0.11
Age	59.3±12.0	56.7±14.0	1.0 (0.98-1.1)	0.55
Grade (Ki-index)	G1 (<2): 3 (37.5%) G2 (2-20): 5 (62.5%) G3 (>20): 0 (0.0%)	71 (59.7%) 42 (35.3%) 6 (5.0%)	1.8 (0.6-5.8)	0.33
Differentiation	Well differentiated: 8 (100%)	Well differentiated: 120 (100%)	2.6 x 10 <sup>7</sup> (0->10 <sup>10</sup> )	>0.99
ENETS TNM	T1N0: 1 (12.5%) - T2N0: 4 (50.0%) T2N1: 1 (12.5%) T3N0: 1 (12.5%) T3N1: 1 (12.5%) - -	T1N0: 59 (50.9%) T1N1: 2 (1.7%) T2N0: 32 (27.6%) T2N1: 5 (4.3%) T3N0: 8 (6.9%) T3N1: 7 (6.0%) T4N0: 1 (0.9%) T4N1: 2 (1.7%)	9.7 (0.6-156.4)	0.11
ENETS Stage	I: 1 (12.5%) IIA: 4 (50.0%) IIB: 1 (12.5%) - IIIB: 2 -	I: 59 (51.3%) IIA: 32 (27.8%) IIB: 9 (7.8%) - IIIB: 14 (12.2%) IV: 1 (0.9%)	7.8 (0.7-86.5)	0.09
Size	32.3±11.9	19.0 (12.0-30.0)	1.0 (0.99-1.1)	0.22
Lymph node	2 (28.6%)	17 (15.0%)	2.3 (0.4-12.4)	0.34
LVI	3 (42.9%)	25 (20.8%)	3.0 (0.6-14.9)	0.18
VI	0 (0.0%)	4 (3.7%)	3.9 x 10 <sup>-8</sup> (0->10 <sup>10</sup> )	>0.99
PNI	1 (14.3%)	14 (13.5%)	2.9 (0.5-15.6)	0.23
Surgery type	Whipple: 2 (25.0%) Central pancreatectomy: 1 (12.5%) Distal pancreatectomy: 1 (12.5%) Distal pancreatectomy+splenectomy: 4 (50.0%) - -	Whipple: 34 (28.3%) Central pancreatectomy: 12 (10.0%) Distal pancreatectomy: 29 (24.2%) Distal pancreatectomy+splenectomy: 30 (25.0%) Enucleation: 14 (11.7%) Distal pancreatectomy+multivisceral excision: 1 (0.01%)	0.4 (0.02-6.1)	0.49
Invasion adjacent organs	0 (0.0%)	3 (2.5%)	1.1 x 10 <sup>-7</sup> (0- >10 <sup>10</sup> )	>0.99

LVI, lymphovascular invasion; VI, vascular invasion; PNI, perineural invasion; HR, hazard ratio; ENETS, European Neuroendocrine Tumor Society