Title page

Pancreatic neuroendocrine tumors: a single-center 20-year experience with 100 patients

A short title:

One hundred patients with pancreatic NEN at a single center

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Abstract:

Background/Objectives: Pancreatic neuroendocrine neoplasms (NENs) are rare tumors, exhibiting several morphological, functional, and behavioral characteristics. However, only few reports have evaluated large case series of pancreatic NEN.

Methods: We conducted a retrospective review of 100 consecutive patients with pancreatic NEN diagnosed pathologically and treated at the National Cancer Center Hospital between 1991 and 2010.

Results: The study included 48 males and 52 females (median age: 55 years). Fourteen patients had clinical symptoms caused by excess hormone secretion at diagnosis. Twelve patients were diagnosed with neuroendocrine tumor (NET) G1, 54 with NET G2, and 32 with neuroendocrine carcinoma (NEC) as per the 2010 World Health Organization classification. Distant metastases were observed in 25%, 43%, and 84% of the patients with NET G1, NET G2, and NEC, respectively. Serum levels of neuron-specific enolase and lactate dehydrogenase significantly increased in patients with NEC compared with those in patients with NET G1/G2. The 5-year survival rates of patients with NET G1, NET G2, and NEC were 91%, 69%, and 10%, respectively. Good performance status (PS), lower stage, and histopathological grade were identified as independent favorable prognostic factors.

Conclusions: Patients with NET G1/G2 treated with surgical resection had a good prognosis. Most patients with NEC exhibited distant metastases and had a poor prognosis. Staging classification and the WHO 2010 grading are important factors for selecting the appropriate treatment strategy and predicting prognosis for patients with pancreatic NEN.

Key words:

pancreatic neuroendocrine tumors, pancreatic neuroendocrine carcinoma, grade, stage, prognosis

Introduction

Pancreatic neuroendocrine neoplasms (NENs) are rare tumors with an annual incidence of 0.32 per 100,000 in the United States [1] and 1.01 per 100,000 in Japan [2]. Pancreatic NEN represents 1%–2% of all pancreatic tumors [3], and the reported incidence in autopsy studies ranges from 0.5% to 10% [3-5]. The clinical manifestations of pancreatic NEN vary, depending on whether they are clinically functioning (i.e., able to produce hormones) or non-functioning. The proportion of non-functioning pancreatic NEN has been reported as approximately 30%–65% of all pancreatic NENs [6, 7]. Non-functioning pancreatic NEN may be asymptomatic or may present with symptoms such as abdominal pain and obstructive jaundice caused by the tumor itself when it becomes large enough to cause compression or invasion of adjacent organs or when the cancer metastasizes. In addition to the status of hormone production, tumor grading based on the assessment of proliferative activity plays an important role in deciding therapeutic approaches for pancreatic neuroendocrine tumors (NETs). Recently, the World Health Organization (WHO) proposed a new classification of pancreatic NEN as NET G1, NET G2, and neuroendocrine carcinoma (NEC) based on proliferation and tumor morphology. Pancreatic NENs, especially NETs, are usually slow-growing tumors and have a better prognosis than other pancreatic tumors, even with metastases. Surgical resection should be recommended if possible [8]. Conversely, current progress of molecular targeted therapy for pancreatic NET has attracted considerable attention. The anticancer agents everolimus and sunitinib have significantly prolonged progression-free

survival in pancreatic NET patients [9, 10]. Although there has been progress in the elucidation of the histogenesis, morphology, immunohistochemistry, molecular biology, and classification of this disease, further research is required because only a few large case series have been investigated. Large case series including unresectable pancreatic NEN pathologically diagnosed are scarce.

Here, we report the clinical features of pancreatic NEN patients treated at a single institution. We aim to clarify the clinical characteristics, treatment strategies, and outcome according to clinicopathological and prognostic factors in pancreatic NEN. Most studies have been performed in western countries and do not account for possible differences between pancreatic NEN patients in North America/Europe and those in other countries. To the best of our knowledge, this is the first report in Asia on a large-scale survey of resectable and unresectable pathologically proven pancreatic NEN.

Methods

Patients and methods

Information about pancreatic NEN patients was obtained from the pathology databases of the National Cancer Center Hospital, Tokyo, Japan for the period between May 1991 and November 2010. The following clinical parameters were assessed from the medical records: age, gender, performance status (PS), medical history, presence of tumor-related symptoms (i.e., abdominal pain and jaundice), presence of clinical symptoms caused by excess hormone secretion (i.e., diarrhea, hypoglycemic episodes, and history of peptic ulcers), laboratory data, including hormone levels and tumor markers [i.e., carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, neuron-specific enolase (NSE), and pro-gastrin-releasing peptide (ProGRP)], selected strategy of cancer treatment, and outcomes. Serum chromogranin A has not been evaluated because it has not been approved in Japan as a biomarker for pancreatic cancer. Radiological findings, such as computed tomography and magnetic resonance imaging, were also reviewed to obtain information pertaining to tumor size, location within the pancreas (head, body, or tail), and metastatic site. TNM staging and tumor grading were conducted according to the European Neuroendocrine Tumor Society (ENETS) [11] and the 2010 WHO classification [12]. Histopathological and immunohistochemical slides of patients with pancreatic NEN were reviewed by a pathologist at the National Cancer Center Research Institute.

This study protocol was approved by the Institutional Review Board and was in accordance

with the ethical guidelines for epidemiological research.

Statistical Analysis

Overall survival (OS) and median survival time (MST) were calculated from the time of initial treatment through last follow-up. Patients who failed to follow-up were treated as censored cases. Survival curves were estimated using the Kaplan–Meier method, and statistical significances were evaluated using a log-rank test. A univariate regression analysis was undertaken to examine potential factors influencing OS. Subsequently, a multivariate analysis was performed using a Cox proportional hazards regression model. Differences in the numerical variables between categorical factors were tested using the Mann–Whitney test. For these exploratory analyses, $P < 0.05$ was considered significant. All statistical analyses were conducted using SPSS statistical software, version 19.

Results

Disease characteristics

One hundred patients with pancreatic NEN were identified between May 1991 and November 2010. The median age of the cohort was 55 years (range, 19–82 years). Forty-eight percent (n = 48) of patients were males and 52% (n = 52) were females (Table 1). Tables 1 and 2 summarize the frequencies of clinical features at the time of diagnosis. Twelve percent (n = 12) of cases presented with abdominal pain and 3% (n = 3) with jaundice. Fourteen percent (n = 14) of the patients presented with clinical symptoms and 86% (n = 86) were asymptomatic. Clinical symptoms caused by excess hormone secretion included uncontrollable peptic ulcers, diarrhea, and hypoglycemia, and their respective proportions were 6% (n = 6), 6% (n = 6), and 2% (n = 2). According to the WHO 2010 classification, 98 of all patients were divided into NET G1, NET G2, and NEC subgroups. Two patients were not classified owing to insufficient histopathological material. Tissue specimens were collected by surgical resection (n = 47) and needle biopsy (n = 53). The proportions of patients in the NET G1, NET G2, and NEC subgroups were 12% (12/98), 55% (54/98), and 33% (32/98) of all patients (n = 100), respectively. Based on the WHO 2010 classification (AJCC, American Joint Committee on Cancer/UICC, International Union Against Cancer), the proportions of patients with pathologic TNM stage IA/B, IIA/B, III, and IV disease were 19%, 26%, 1%, and 54% of all patients. Based on the ENETS classification, stage I, IIA/B, IIIA/B, and IV were 13%, 12%, 21%, and 54%, respectively. Furthermore, distant metastases were observed in 25%

(3/12), 43% (23/54), and 84% (27/32) of patients in NET G1, NET G2, and NEC subgroups, respectively. The proportion of patients with elevated tumor markers (CEA, CA19-9, NSE, and/or ProGRP) and lactate dehydrogenase (LDH) tended to increase with the pathological grade (Figure 1). Serum levels of NSE and LDH differed significantly between NET G1/G2 and NEC groups (Figure 1A and Figure 1E). We found a positive correlation between the Ki67 index and NSE levels ($r = 0.303$, $p = 0.021$) and LDH levels ($r = 0.578$, $p < 0.001$).

Treatment strategy

Surgical resection was performed in 75% (9/12), 57% (31/54), and 22% (7/32) of patients belonging to NET G1, NET G2, and NEC subgroups, respectively. All of the patients in NET G1 subgroup, who underwent resection, were kept under observation without further treatment, and no evidence of recurrence was seen. Twenty-five percent (3/12), 31% (17/54), and 66% (21/32) of patients in NET G1, NET G2, and NEC subgroups received systemic chemotherapy as the initial treatment. Systemic chemotherapy was included in the entire treatment course in 25% (3/12), 47% (25/54), and 78% (25/32) of patients in NET G1, NET G2, and NEC subgroups, respectively. The proportion of patients in NET G1, NET G2, and NEC subgroups receiving only palliative care immediately after diagnosis was 0%, 4% (2/54), and 13% (4/32), respectively. Notably, patients in NET G2 subgroup received various treatments. The proportion of patients in NET G2 subgroup who were administered chemoradiotherapy, octreotide,

and transcatheter arterial embolization as an initial treatment was 2% (1/54), 2% (1/54), and 4% (2/54), respectively (Table 2).

Outcome according to clinicopathological factors

The median survival period of the 100 patients in this study was 10.5 years (95% confidence interval, 0.39 to 20.6). The 2-year, 5-year, and 10-year survival rates of all patients were 61.1%, 53.3%, and 50.7%, respectively (Figure 2).

Tables 3-4 and Figures 3-4 show survival periods according to clinicopathological factors including stage, grade, PS, distant metastasis, and initial treatment. A tendency of difference was observed between the WHO 2010 grading classification (NET G1, NET G2, and NEC) in the subgroup of patients that received surgical resection or systemic chemotherapy, and patients with stage I, II, III, and IV the AJCC/UICC and ENETS Cancer classification. A tendency of difference was also observed between two staging systems in a subgroup of pancreatic NEN patients. The 5-year survival rates were 100%, 76.2%, and 9.3% for AJCC stage I, II/III, and IV patients, respectively ($P < 0.01$, stage I versus stage II/III; $P < 0.01$, stage II/III versus stage IV, Figure 3A). AJCC stage IIA/B and stage III patients were analyzed together because there was only one stage III patient. The 5-year survival rates were 100%, 91.7%, 74.2, and 9.3% for ENETS stage I, II, III, and IV patients, respectively ($P = 0.24$, stage I versus stage II; $P = 0.16$, stage II versus stage III; $P < 0.01$, stage III versus stage IV, Figure 3B). Furthermore,

the 5-year survival rates were 90.9%, 69.0%, and 9.9% for NET G1, NET G2, and NEC patients, respectively (P = 0.30, NET G1 versus NET G2; P < 0.01, NET G2 versus NEC, Figure 4).

Prognostic factors

Age, gender, PS, primary site, functionality, stage, and grade were evaluated for their association with patient survival. Among all 100 pancreatic NEN patients, the following pretreatment variables were identified as being significantly associated with survival based on univariate analyses: PS (P < 0.01), AJCC/UICC stage (P < 0.01), ENETS stage (P < 0.01), and grade (P < 0.01; Table 4). Subsequently, three of the above four factors were identified as independent prognostic factors in a Cox multivariate regression analysis: PS (P < 0.01), grade (P < 0.01), and AJCC/UICC stage (P < 0.01).

Discussion

In the present study, we have investigated the treatment outcomes of 100 patients with pancreatic NEN treated at a single cancer center over the past two decades. The proportion of patients with non-functioning tumor (86%) and NEC (32%) was higher than that observed in previous reports [6, 7, 13]. Improvement of imaging diagnostic technology and increasing chances of screening may contribute greatly to the detection of non-functioning pancreatic NEN. The proportion of patients with stage I (19%), II (26%), III (1%), and IV (54%) disease, or patients with NET G1 (12%), NET G2 (54%), and NEC (32%) were partly different from published studies. A recent large case series report revealed that there are 15%–20%, 10%–16%, 4%–7%, and 61%–66% of patients with stage I, II, III and IV disease, respectively [13-15], and 73%, 16%, and 8% patients with NET G1, NET G2, and NEC [13], respectively. The stage-stratified survival rates derived from our institutional database are markedly lower than those extrapolated from national population registries. One potential confounding factor is the difference in the rates of NEC cases between previous reports and the present data (8% vs. 32%). This may be due to the fact that our institution is a cancer specialized center, gathering patients with more aggressive tumors (institutional referral bias). In addition, all of the patients in this study had pathologically proven NEN: clinically diagnosed NEN cases with no pathological diagnosis were not included in this study. Although this selection criterion ensured the quality of diagnosis, it might have caused selection bias by eliminating clinically diagnosed indolent NET patients who did not receive anticancer treatment.

Chromogranin A (CgA), which has not been approved in Japan, is an efficient marker for pancreatic NEN [16], although it has been reported that serum levels of CgA are elevated in patients using proton pump inhibitor (PPI) [17, 18]. Instead of CgA, serum NSE, ProGRP, and LDH have been frequently evaluated for this disease in Japan, and this study indicates that they might be a good alternative to CgA, especially in NEC, and could provide useful information for identifying NET or NEC. So far, there are no reports to show that PPI affects serum levels of these markers.

Interestingly, distant metastases of patients with NET G1 occurred in a certain proportion of our cohort, similar to previous studies [10, 19]. Thus, we conclude that all NENs including NET G1 have malignant potential. Therefore, patients with NET G1 should be examined for distant metastases. In the absence of metastasis, radical resection should be recommended and would provide extremely good prognosis as shown in the present study (Table 3). Our results support standard therapy options in accordance with the guidelines.

The benefits of resection as the primary curative option in patients with pancreatic NEN are generally not doubted. In our study, 75% of NET G1 and 57% of NET G2 patients underwent surgical resection and had good prognosis; however, 22% of NEC patients underwent surgery and showed relatively poor prognosis (Table 3B). The 5-year survival rates and MST for NEC patients who underwent surgery were 35.7% and 2.0 years, respectively; previous report showed 5-year survival rates of 28.3% and MST of approximately 2.0 years [20]. The main reason for the difference in survival

between our results and previous reports may be owing to the fact that 4 out of 7 NEC patients who underwent radical surgery as an initial treatment had stage IV disease (OS times were 9.6 months, 13 months, 18 months, and 24 months). Current guidelines do not recommend resection for NEC with distant metastases [21,22], and the poor prognosis we observed in NEC patients in our study supports these guidelines.

Multivariate analysis showed that poor PS, poor tumor grade, and advanced stage were significant prognostic factors of poor prognosis and these results were clinically reasonable. Various prognostic factors were reported in earlier reports; however, stage and grade have emerged as the most potent predictive markers [23-29]. The present study also indicated that tumor grade is a critically important prognostic factor, with a hazard ratio for death of 1.05 in patients with NET G2 versus those with NET G1 and of 4.43 in patients with NEC versus those with NET G1 (Table 4). Our data indicate that the WHO 2010 TNM stage (AJCC/UICC) is also prognostic for OS and can be adopted in clinical practice. Two TNM staging systems are currently used: one is proposed by AJCC, which is the same as the WHO classification, and the other is proposed by the ENETS guidelines. A large series investigation of pancreatic NEN was conducted [13, 30,31] to determine which staging system was superior in terms of performance in clinical practice. The WHO 2010 classification (AJCC/UICC) system is intuitive and easily adoptable by clinicians and pathologists already familiar with the TNM staging system used for pancreatic adenocarcinomas. We also analyzed this cohort using the ENETS stage classification.

Similarly, the ENETS classification is prognostic for the survival of patients with pancreatic NEN [31]. However, the superiority of staging systems cannot be evaluated because of the small size of our cohort.

In the distinctive point on between Japanese and the western background, age at diagnosis in our study is lower than that reported previously (55 years vs. 60 years) using the SEER database [1]. Concerning the disease stage, the rate of pancreatic NENs with distant metastases in our study is less than that reported previously (54% vs. 64%). Furthermore, the median survival time of patients with localized (corresponding to AJCC/UICC stage I), regional (stage II and III), and distant (stage IV) metastases is as follows: not reached vs. 11.3 years, 10.5 years vs. 6.4 years, and 1.3 years vs. 2.0 years, respectively. The median survival time of patients without distant metastasis tended to be longer. However, the poorer prognosis of patients with distant metastasis (stage IV) in our study compared with the previous study is because 27 patients with stage IV pancreatic NEC (27% of all patients in our study), who had the poorest prognosis of pancreatic NEN, were included in our study, and the prognosis of patients with pancreatic NEC with distant metastasis (median survival time: 0.7 years) could contribute to the median survival time of patients with pancreatic NEN with distant metastasis.

In conclusion, our institutional retrospective analysis of 100 patients with pancreatic NEN demonstrated the clinicopathological features of the disease. PS, tumor grade, and metastasis for pancreatic NEN are significant prognostic factors for OS. Appropriate selection of treatment based on the evaluation of tumor grade and stage as well as the precise pathological diagnosis plays a major role in the

clinical management of patients with pancreatic NEN.

Disclosure Statement

The authors have no conflicts of interest.

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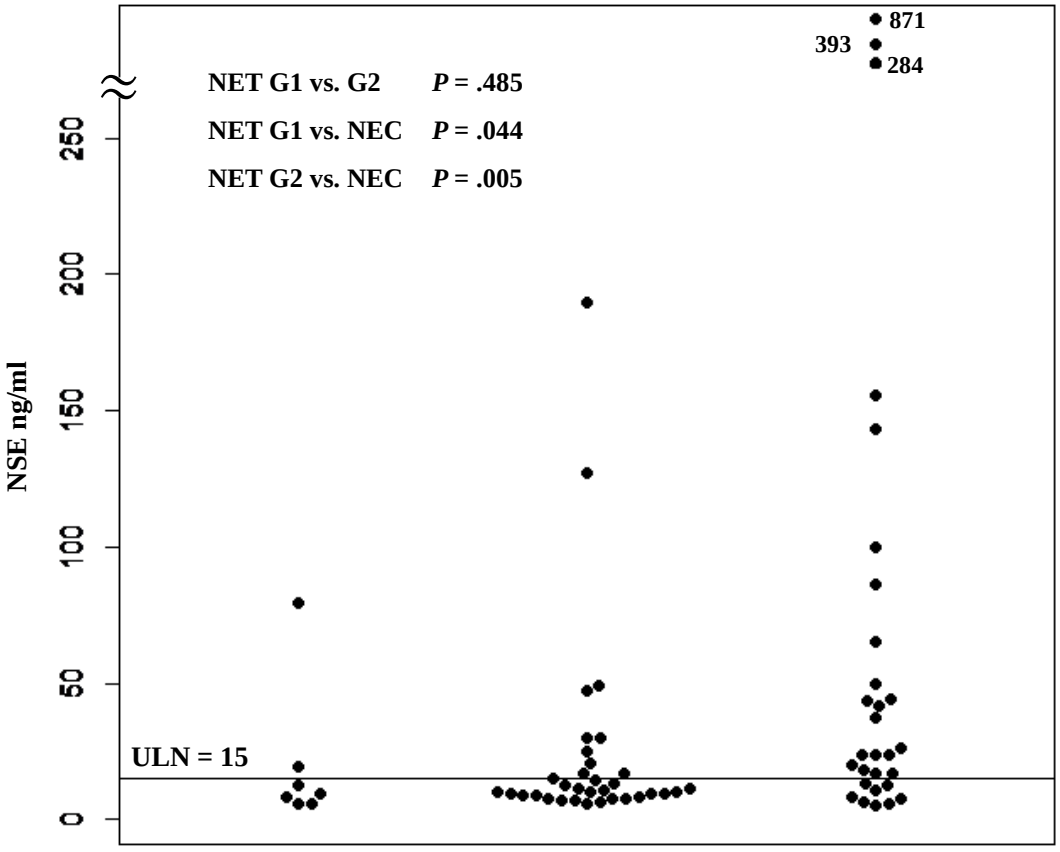
Figure 1A

NSE



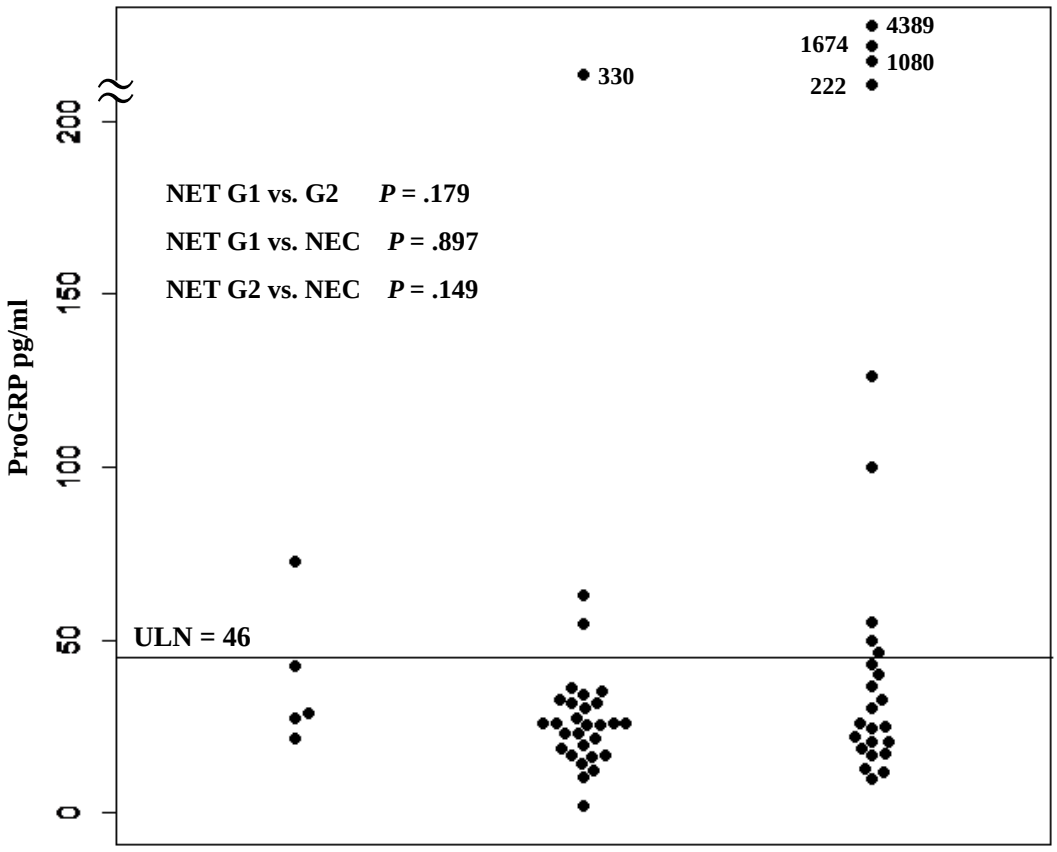
	NET G1	NET G2	NEC
	no. (%)	no. (%)	no. (%)
Elevated	2 (29)	10 (30)	21 (72)
Not elevated	5 (71)	23 (70)	8 (28)

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; NSE, neuron specific enolase; ULN, upper limit of the normal

Comparisons are made by Mann–Whitney tests. The line represents the upper limit of normal.

Figure 1B

ProGRP



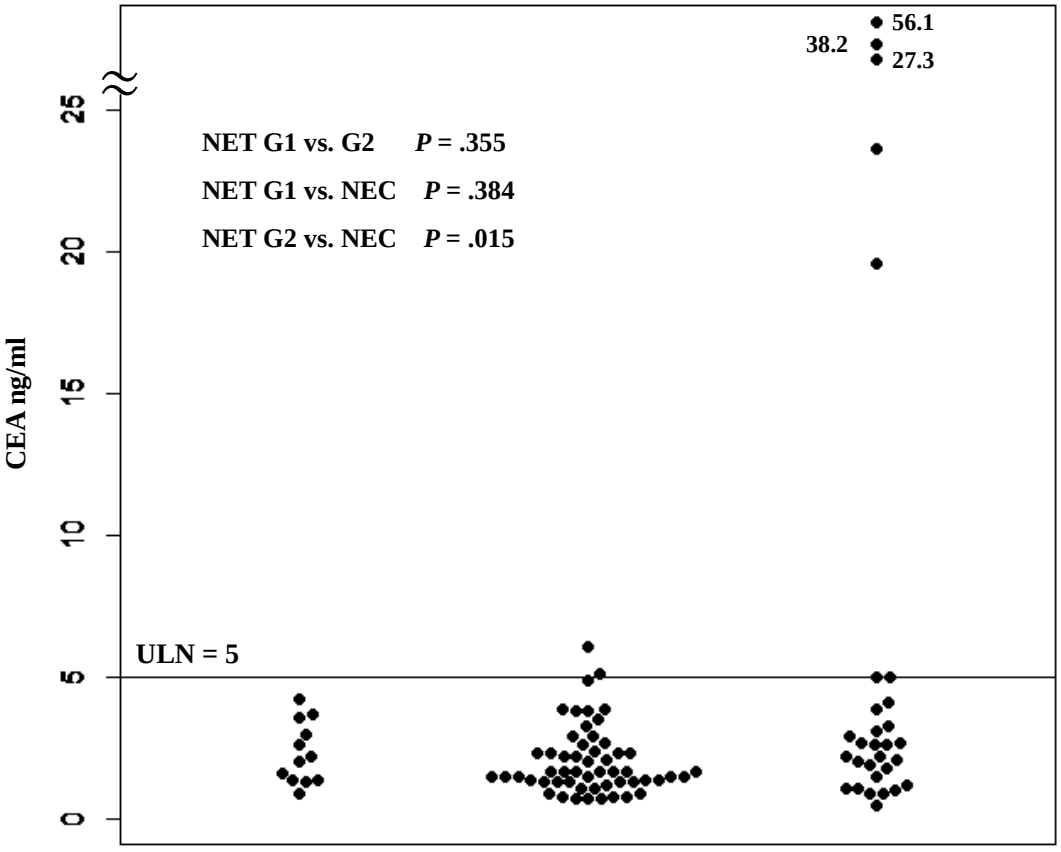
	NET G1 no. (%)	NET G2 no. (%)	NEC no. (%)
Elevated	1 (20)	3 (10)	9 (35)
Not elevated	4 (80)	26 (90)	17 (65)

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; ProGRP, pro-gastrin-releasing peptide; ULN, upper limit of normal

Comparisons are made by Mann–Whitney tests. The line represents the upper limit of normal.

Figure 1C

CEA



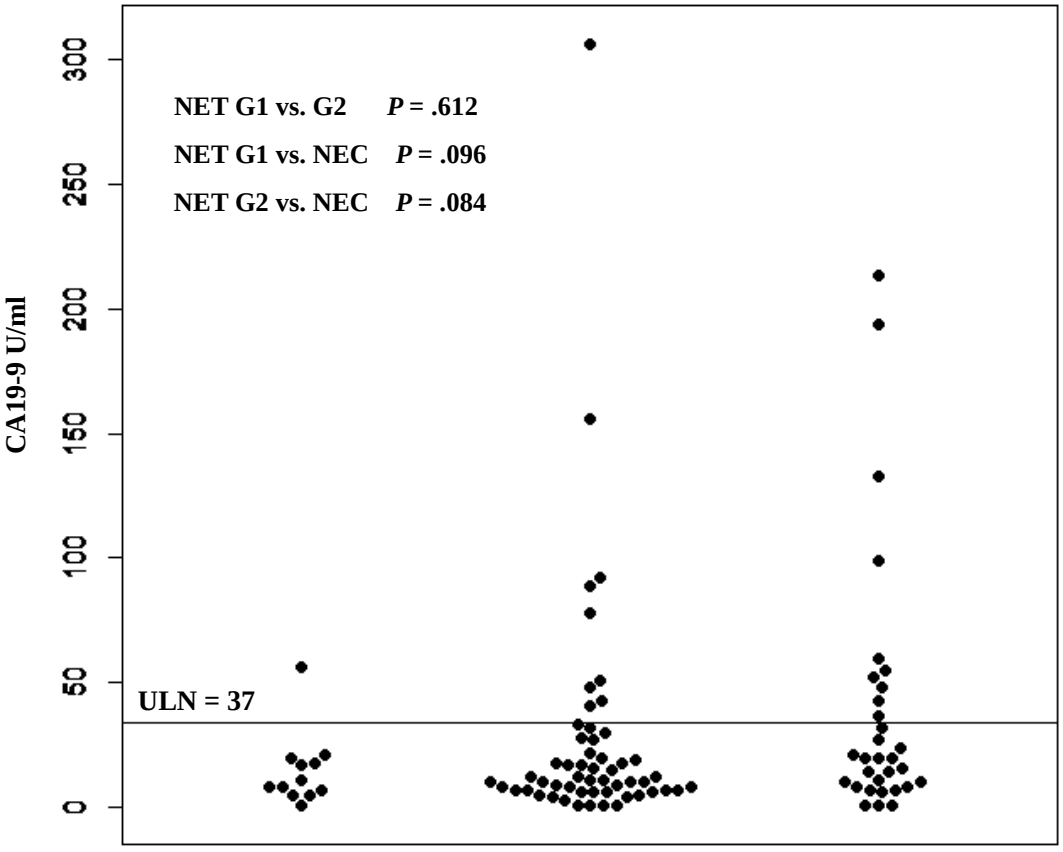
	NET G1	NET G2	NEC
	no. (%)	no. (%)	no. (%)
Elevated	0 (0)	2 (4)	7 (23)
Not elevated	12 (100)	52 (96)	23 (77)

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; CEA, carcinoembryonic antigen; ULN, upper limit of normal

Comparisons are made by Mann–Whitney tests. The line represents the upper limit of normal.

Figure 1D

CA19-9



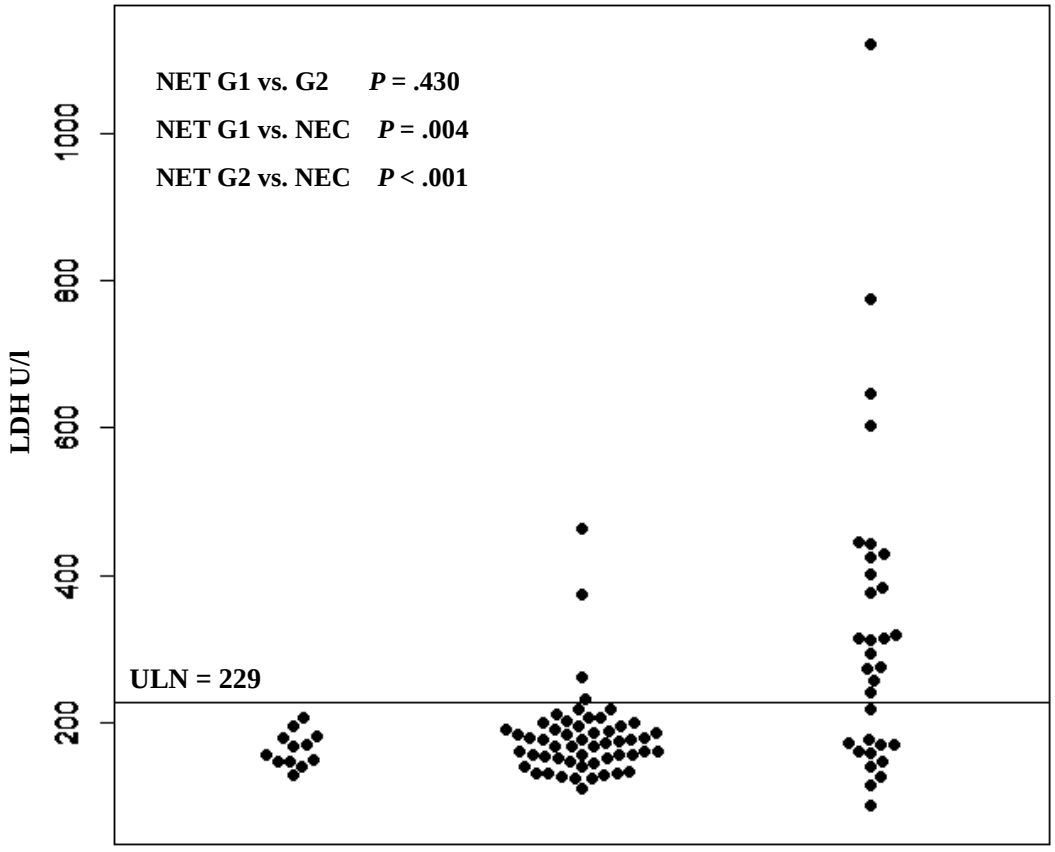
	NET G1	NET G2	NEC
	no. (%)	no. (%)	no. (%)
Elevated	1 (8)	9 (17)	10 (32)
Not elevated	11 (92)	45 (83)	21 (68)

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; CA19-9, carbohydrate antigen 19-9; ULN, upper limit of normal

Comparisons are made by Mann–Whitney tests. The line represents the upper limit of normal.

Figure 1E

LDH



	NET G1	NET G2	NEC
	no. (%)	no. (%)	no. (%)
Elevated	0 (0)	4 (7)	20 (63)
Not elevated	12 (100)	50 (93)	12 (37)

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; LDH, lactate dehydrogenase; ULN, upper limit of normal

Comparisons are made by Mann–Whitney tests. The line represents the upper limit of normal.

Table 1 Patient characteristics

Factors		No. (n = 100)
Sex	Male	48
	Female	52
Age, years	Median (range)	55 (19–82)
Performance status	0	63
	1	30
	2	7
Primary tumor	Head	54
	Body	25
	Tail	21
Signs	Abdominal pain	12
	Jaundice	3
	Anorexia	2
Clinical symptoms[†]	Ulcer	6
	Diarrhea	6
	Hypoglycemia	2
NSE (ng/ml)	Median (range)	14.6 (5.3–871)
ProGRP (pg/ml)	Median (range)	26.1 (2.3–4389)
CEA (ng/ml)	Median (range)	2.0 (0.5–56.1)
CA19-9 (U/ml)	Median (range)	12.0 (1.0–306)
LDH (U/l)	Median (range)	177 (88–1121)
AJCC/UICC stage	I A/B	19
	II A/B	26
	III	1
	IV	54
ENETS stage	I	13
	II A/B	12
	III A/B	21
	IV	54
Grading	NET G1	12
	NET G2	54
	NEC	32
	Unknown	2

[†] Owing to excess hormone secretion

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; ENETS, European Neuroendocrine Tumor Society

Table 2

Patient characteristics according to the WHO 2010 grading system

Factors		NET G1 n = 12 (%)	NET G2 n = 54 (%)	NEC n = 32 (%)
Clinical symptoms[†]	Ulcer	0	4 (7.4)	1 (3.1)
	Hypoglycemia	0	2 (3.7)	0
	Diarrhea	1 (8.3)	4 (7.4)	1 (3.1)
	Any	1 (8.3)	10 (19)	2 (6.3)
AJCC/UICC stage	I A/B	5 (42)	14 (26)	0
	II A/B	4 (33)	17 (31)	5 (15)
	III	0	0	0
	IV	3 (25)	23 (43)	27 (84)
ENETS stage	I	4 (33)	9 (17)	0
	II A/B	3 (25)	9 (17)	0
	III A/B	2 (17)	13 (24)	5 (16)
	IV	3 (25)	23 (43)	27 (84)
Initial treatment	Resection	9 (75)	31 (57)	7 (22)
	Chemotherapy	3 (25)	17 (30)	21 (66)
	Chemoradiotherapy	0	1 (2)	0
	Octreotide	0	1 (2)	0
	TAE	0	2 (4)	0
	Palliative care	0	2 (4)	4 (13)
Chemotherapy (all clinical courses)		3 (25)	25 (47)	25 (78)

[†]Owing to excess hormone secretion

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; TAE, transcatheter arterial embolization; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; ENETS, European Neuroendocrine Tumor Society

Table 3A Median, 2-year, and 5-year survival rates of NET G1, NET G2, and NEC, respectively, according to distant metastasis

		n	Median (years)	2-year (%)	5-year (%)	*P* (log-rank)
M0	NET G1	10	10.5	100	100	0.003
	NET G2	31	Not reached	96.8	89.5	
	NEC	5	0.9	40.0	40.0	
M1	NET G1	4	1.1	0	0	<0.0001
	NET G2	23	2.6	54.1	21.6	
	NEC	27	0.7	7.5	0	

M0, no distant metastasis; M1, distant metastasis

Table 3B Median, 2-year, and 5-year survival rates of NET G1, NET G2, and NEC, respectively, according to treatment

		n	Median (years)	2-year (%)	5-year (%)	*P* (log-rank)
Surgery	NET G1	9	10.5	100	100	<0.0001
	NET G2	31	Not reached	100	92.4	
	NEC	7	2.0	35.7	35.7	
Chemotherapy	NET G1	3	1.1	0	0	0.001
	NET G2	25	1.9	31.3	0	
	NEC	25	0.6	0	0	

Table 4

Univariate and multivariate analyses of factors contributing to overall survival

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (continuous)	1.02	0.99–1.05	0.085	-	-	-
Sex (male vs. female)	0.70	0.38–1.28	0.235	-	-	-
Primary site			0.982	-	-	-
Head vs. Body	0.94	0.43–2.04	0.870	-	-	-
Head vs. Tail	0.99	0.41–2.39	0.977	-	-	-
Function vs. Non-function	1.71	0.76–3.86	0.197	-	-	-
PS			<0.001			<0.001
PS 0 vs. 1	3.67	1.91–7.06	<0.001	2.53	1.24–5.20	0.011
PS 0 vs. 2	7.60	2.73–21.1	<0.001	7.99	2.69–23.7	<0.001
Grade			<0.001			<0.001
NET G1 vs. G2	2.06	0.46–9.24	0.346	1.05	0.21–5.15	0.957
NET G1 vs. NEC	15.5	3.48–69.3	<0.001	4.43	0.87–22.5	0.072
AJCC/UICC stage I–II vs. III–IV	10.0	4.21–23.9	<0.001	4.10	1.47–11.4	0.007
ENETS stage I–II vs. III–IV	24.5	3.35-179.0	0.002	6.01	0.70–51.7	0.103

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; CI, confidence interval; HR, hazard ratio; PS, performance status; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; ENETS, European Neuroendocrine Tumor Society