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Long-term outcomes and prognostic factors in 78 Japanese patients with advanced pancreatic neuroendocrine neoplasms: a single-center retrospective study

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Abstract

Objective: Despite an increase in the number of Japanese patients with pancreatic neuroendocrine neoplasms, long-term outcomes and prognostic factors, especially for those with advanced disease, remain unclear.

Methods: We retrospectively reviewed the medical records of 78 patients with unresectable pancreatic neuroendocrine neoplasms treated at our hospital from January 1987 to March 2015. Survival analyses were performed using Kaplan–Meier methods. Prognostic significance of several clinicopathological factors were analyzed by univariate and multivariate analyses using a Cox regression model.

Results: Median overall survivals of pancreatic neuroendocrine tumor ($n = 64$) and pancreatic neuroendocrine carcinoma ($n = 14$) were 83.7 and 9.1 months, respectively (hazard ratio: 0.02, 95% confidence interval: 0.01–0.08, $P < 0.001$). Although no significant differences were observed using a Ki-67 cut-off value of 2% (hazard ratio: 0.46, 95% confidence interval: 0.16–1.13, $P = 0.0989$), a Ki-67 cut-off of 10% was a significant predictor in patients with pancreatic neuroendocrine tumor (hazard ratio: 9.95, 95% confidence interval, 3.01–32.97, $P < 0.001$). Treatment after the advent of targeted therapy (hazard ratio: 0.07, 95% confidence interval: 0.03–0.19, $P < 0.001$) and the presence of bone metastases (hazard ratio: 4.38, 95% confidence interval: 1.42–11.29, $P = 0.013$) were significant prognostic factors in patients with pancreatic neuroendocrine tumor evaluated by univariate analysis. Multivariate analysis also revealed that a Ki-67 index ≥10% (hazard ratio: 38.8, 95% confidence interval: 8.42–226.62, $P < 0.001$), approval of targeted therapy (hazard ratio: 0.02, 95% confidence interval: 0.00–0.11, $P < 0.001$) and bone metastases (hazard ratio: 5.56, 95% confidence interval: 1.10–24.00, $P = 0.039$) were independent prognostic factors.

Conclusions: We elucidated the long-term outcomes and prognostic factors in Japanese patients with advanced pancreatic neuroendocrine neoplasms.

Key words: pancreatic neuroendocrine neoplasms, pancreatic neuroendocrine tumor, pancreatic neuroendocrine carcinoma, Ki-67 index, prognostic factor

Introduction

Pancreatic neuroendocrine neoplasms (PNEN) are rare tumors arising from neuroendocrine cells of the pancreas (1,2). Although recent epidemiological surveys showed an increase in the incidence and prevalence of PNEN in Japan (3) and Western nations (4–7), there were no approved therapeutic agents in Japan for patients with advanced PNEN until everolimus (8) and sunitinib (9) became available recently. These targeted therapeutic agents have been reported to provide clinical benefits in Japanese patients with advanced PNEN (10,11). However, there has been a lack of evidence on the long-term outcomes of Japanese patients with PNEN.

PNEN are usually more indolent and less aggressive than pancreatic ductal adenocarcinoma (1,2). This is partially true for patients in the early stages of disease. However, patients with metastatic disease are known to have a poor prognosis. According to Yao et al. (4), the median survival time for PNEN patients with distant metastases was 24 months. This result is consistent with several reports (12–14), but differs from other reports showing median survival times of 48–90 months (15–18). Similarly, the 5-year survival rates reported in previous studies (5,14–27) also vary greatly, from 18 to 61%, mainly due to the heterogeneity of PNEN.

Ki-67 index is known to affect the long-term outcome of PNEN. The recent World Health Organization (WHO) classification system in 2010 (28) classified neuroendocrine neoplasms (NEN) into different stages according to the Ki-67 labeling index. A Ki-67 cut-off value of 20% to separate neuroendocrine tumors (NET) and neuroendocrine carcinoma (NEC), and 2% to separate G1 and G2 grade NET. The validity of the cut-off value of 2% is supported by results from several studies (17,23,29–32). However, other studies have suggested a cut-off of 5% (18,25,33–36) or 10% (37–39) resulting in a better separation of the prognosis of the G1 and G2 NET grades. Despite these promising results, due to the lack of comparative analyses of primary tumors and disease stage, the prognostic value of the Ki-67 index in advanced stages still needs to be validated (40).

Although a number of studies have been performed to identify the prognostic factors of NEN, most included various disease stages and primary tumor sites. There is limited data focusing on advanced PNEN with some studies reporting various important prognostic factors including: the presence of diffuse liver metastases (14,15,41), bone metastases (41,42), extrahepatic metastases (15), functional status (15), histological grade (16,18), high levels of serum chromogranin A levels (18) and the presence of the primary site (14,41,42). Prognostic factors have varied markedly in different Western studies of patients with advanced PNEN and which factors are important in Japanese patients with advanced PNEN have not yet been identified.

Due to the heterogeneity of PNEN, findings from previous studies, including long-term outcomes, prognostic factors and Ki-67 index cut-off values, might not be relevant for Japanese patients with advanced PNEN. Therefore, we conducted this retrospective study to clarify the long-term outcomes and prognostic factors, including Ki-67 index cut-off values, in Japanese patients with advanced PNEN.

Patients and methods

We retrospectively reviewed data from the medical records of 78 patients with histologically confirmed advanced (unresectable and/or metastatic) PNEN treated at the Kyushu University Hospital between January 1987 and March 2015.

Initial screening and radiological follow up were performed using enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Bone scintigraphy was performed when the bone metastases were suggested by CT and/or MRI findings.

Patients were classified into three groups according to the 2010 WHO classification (28): NET G1, NET G2 and NEC. The Ki-67 index was calculated as a percentage of Ki-67 positive cells in 500–2000 neoplastic cells in areas of strongest nuclear labeling. Evaluation of Ki-67 index was performed using resected specimen of primary site in 44 patients, and core needle biopsy specimen from liver metastases and primary site in 18 and 5 patients, and endoscopic ultrasound-guided fine-needle aspiration (EUS–FNA) specimens from primary site in three patients, respectively. Ten recurrent patients after curative resection underwent core needle biopsy from liver metastases, however, Ki-67 index evaluated from resected specimens were used for further analysis. The Ki-67 index was not available in eight cases, which were then classified according to the 2000 WHO classification (43). Among them, well-differentiated tumors with benign behavior ($n = 7$) and poorly differentiated tumors (small-cell morphology, $n = 1$) were defined as 'NET' and 'NEC', respectively. These patients were excluded from analyses requiring exact Ki-67 values.

Absolute survival time was measured from the time of diagnosis of unresectable disease until death from any cause or latest follow-up. The Kaplan–Meier method was used to estimate overall median survival rates and 95% confidence intervals (CI). The log-rank test was used to compare survival curves. A univariate analysis of survival was performed using a Cox proportional-hazard model to assess the predictive effect of several clinicopathological factors. Variables with a P value < 0.20 in univariate analysis were examined in a multivariate Cox analysis. Patients with pancreatic neuroendocrine carcinoma (PNEC) have been reported in a number of studies to have a more aggressive malignancy than PNET with G1 or G2 (18,19,22,30,33,35,44). We therefore excluded these patients from univariate and multivariate analyses. All analyses were performed using SAS software (version 11, SAS Institute, Cary, NC, USA). This study was approved by the Institutional Review Board of Kyushu University Hospital.

Results

Patient characteristics

A total of 78 patients with advanced PNEN were enrolled in this study (Table 1). The median age was 55 (range 21–85), with a gender ratio of almost 1:1. The vast majority of patients (74%) had non-functioning tumors. The tumors of 13 patients (17%) were associated with inherited syndromes, 11 of which were multiple endocrine neoplasia type 1. Of 33 patients (42%) with a history of curative resection for primary or metastatic sites, 6 patients underwent several resections. The liver was the most common metastatic site (83%); 54 patients with liver metastases had multiple (≥5) lesions. Of 8 patients (10%) with bone metastases, spinal cord compression, pathologic fracture and pain due to bone metastasis were detected in 1, 2 and 4 patients, respectively.

Table 1. Patient characteristics

	Overall ($n = 78$)	PNET ($n = 64$)	PNEC ($n = 14$)
Age, median (range)	55 (21–85)	56 (21–85)	62 (35–82)
Gender, no. (%)			
Male	40 (51)	33 (52)	7 (50)
Female	38 (49)	31 (48)	7 (50)
Hormonal production, no (%)			
Non-functioning	58 (74)	44 (69)	14 (100)
Functioning[a]	20 (26)	20 (31)	0
Hereditary status, no. (%)			
Sporadic	65 (83)	52 (81)	13 (93)
MEN type 1	11 (14)	11 (17)	0
Von Hippel Lindau	2 (3)	1 (2)	1 (7)
WHO classification, no. (%)			
NET G1	20 (26)	20 (31)	–
NET G2	37 (47)	37 (58)	–
NET G3 (NEC)	13 (17)	–	13 (93)
Unknown[b]	8 (10)	7 (11)	1 (7)
Previous curative resection[c], no. (%)			
Yes	33 (42)	29 (45)	4 (29)
No	45 (58)	35 (55)	10 (71)
No. of disease sites, no. (%)			
1	24 (31)	21 (33)	3 (21)
2	25 (32)	20 (31)	5 (36)
≥3	29 (37)	23 (36)	6 (43)
Organ involved[d], no. (%)			
Liver	65 (83)	54 (84)	11 (79)
diffuse (≥5 lesions)	54 (69)	45 (70)	9 (64)
Pancreas	47 (60)	36 (56)	11 (79)
Lymph nodes	42 (54)	35 (55)	7 (50)
Bone	8 (10)	8 (13)	0
Dissemination	7 (9)	7 (11)	0
Lung	3 (4)	1 (2)	2 (14)
Others	4 (5)	2 (3)	2 (14)

MEN, multiple endocrine neoplasia; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PNEC, pancreatic neuroendocrine carcinoma; PNET, pancreatic neuroendocrine tumors; VIP, vasoactive intestinal peptide; WHO, World Health Organization.

[a]Included 13 gastrinomas, 3 insulinomas, 2 VIPomas, 1 glucagonoma and somatostatinoma.

[b]Well-differentiated ($n = 7$) and poorly differentiated tumors ($n = 1$) were defined as 'PNET' and 'PNEC', respectively. These eight patients were excluded from the analysis that required the exact value of Ki-67 index.

[c]Included curative resection for primary and/or metastatic sites before the diagnosis of unresectable.

[d]Organ involved at the time of diagnosis as unresectable and/or metastatic.

Treatment

Treatment data were available for 77 patients. Of these, all patients received some form of treatment except for one patient in the NEC group, who was treated with best supportive care (Table 2). The indications for each therapeutic modality were based on the doctor's discretion. The most common therapeutic modalities for PNET patients were targeted therapy (73%), somatostatin analog (67%), liver-directed therapy (47%) and chemotherapy (45%). Of the patients treated with targeted therapy, everolimus and sunitinib were given to 50 and 23 patients, respectively. Due to the lack of effective chemotherapy regimens, gemcitabine- and 5-fluorouracil-based chemotherapies, approved for pancreatic ductal adenocarcinoma, were frequently given for patients with PNET. As streptozocin was not approved in Japan until 2015, 3 of 8 patients were treated with off-label use of streptozocin. None of these patients received temozolomide-based chemotherapy, which has been reported to be effective in patients with PNET (45,46).

Table 2. Treatment for pancreatic neuroendocrine neoplasms

	Overall ($n = 78$) no. (%)	PNET ($n = 64$) no. (%)	PNEC ($n = 14$) no. (%)
Targeted therapy	53 (68)	47 (73)	6 (43)
Everolimus	50 (64)	45 (70)	5 (36)
Sunitinib	23 (29)	20 (31)	3 (21)
Somatostatin analog	47 (60)	43 (67)	4 (29)
Chemotherapy	40 (51)	29 (45)	11 (79)
Platinum-based regimens	19 (24)	8 (13)	11 (79)
GEM-based regimens	18 (23)	16 (25)	2 (14)
5-FU-based regimens	13 (17)	12 (19)	1 (7)
STZ-based regimens	8 (10)	8 (13)	0
Others	6 (8)	5 (8)	1 (7)
No. of regimens			
1 regimen	24 (31)	16 (25)	8 (57)
2 regimens	12 (15)	10 (16)	2 (14)
≥3 regimens	4 (5)	3 (5)	1 (7)
Liver-directed therapy (TACE and/or RFA)	31 (40)	30 (47)	1 (7)
1–2 time	21 (27)	20 (31)	1 (7)
310 times	7 (9)	7 (11)	0
≥11 times	3 (4)	3 (5)	0
Aggressive surgery[a]	18 (23)	17 (27)	1 (7)
Pancreas	11 (14)	11 (17)	0
Liver	5 (6)	5 (8)	0
Others	5 (6)	4 (8)	1 (7)
Radiation	4 (5)	4 (6)	0
PRRT	3 (4)	3 (5)	0
Others	2 (3)	2 (3)	0
Best supportive care	1 (1)	0	1 (7)
Unknown	1 (1)	1 (2)	0

5-FU, 5-fluorouracil; GEM, gemcitabine; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; STZ, streptozocin; TACE, transarterial chemoembolization.

[a]Non-curative resection for primary site and/or metastatic sites.

Of 14 patients with PNEC, 11 patients (79%) received chemotherapy. Of these, all were treated with platinum-based chemotherapies. In addition, six patients (43%) were treated with targeted therapy; five and three patients with everolimus and sunitinib, respectively.

Survival

The median overall survival in patients with PNET (83.7 months, 95% confidence interval [CI]: 45.2–154.4 months) was significantly longer than with PNEC (9.1 months, 95% CI: 4.3–16.5 months, hazard ratio [HR]: 0.02, $P < 0.001$) (Fig. 1a). The 1-, 3-, 5- and 10-year survival rates were 89, 74, 56 and 33% in the PNET group, respectively, and 34, 17, 0 and 0% in the PNEC group, respectively.

Ki-67 cut-off value

Of 57 patients with PNET whose Ki-67 index were available and under 20%, survival analyses were performed using cut-off values of 2, 5 and 10% (Fig. 1 b–d). Although 2% (HR: 2.19, 95% CI: 0.88–6.16, $P = 0.099$) and 5% (HR: 2.12, 95% CI: 0.85–5.36,

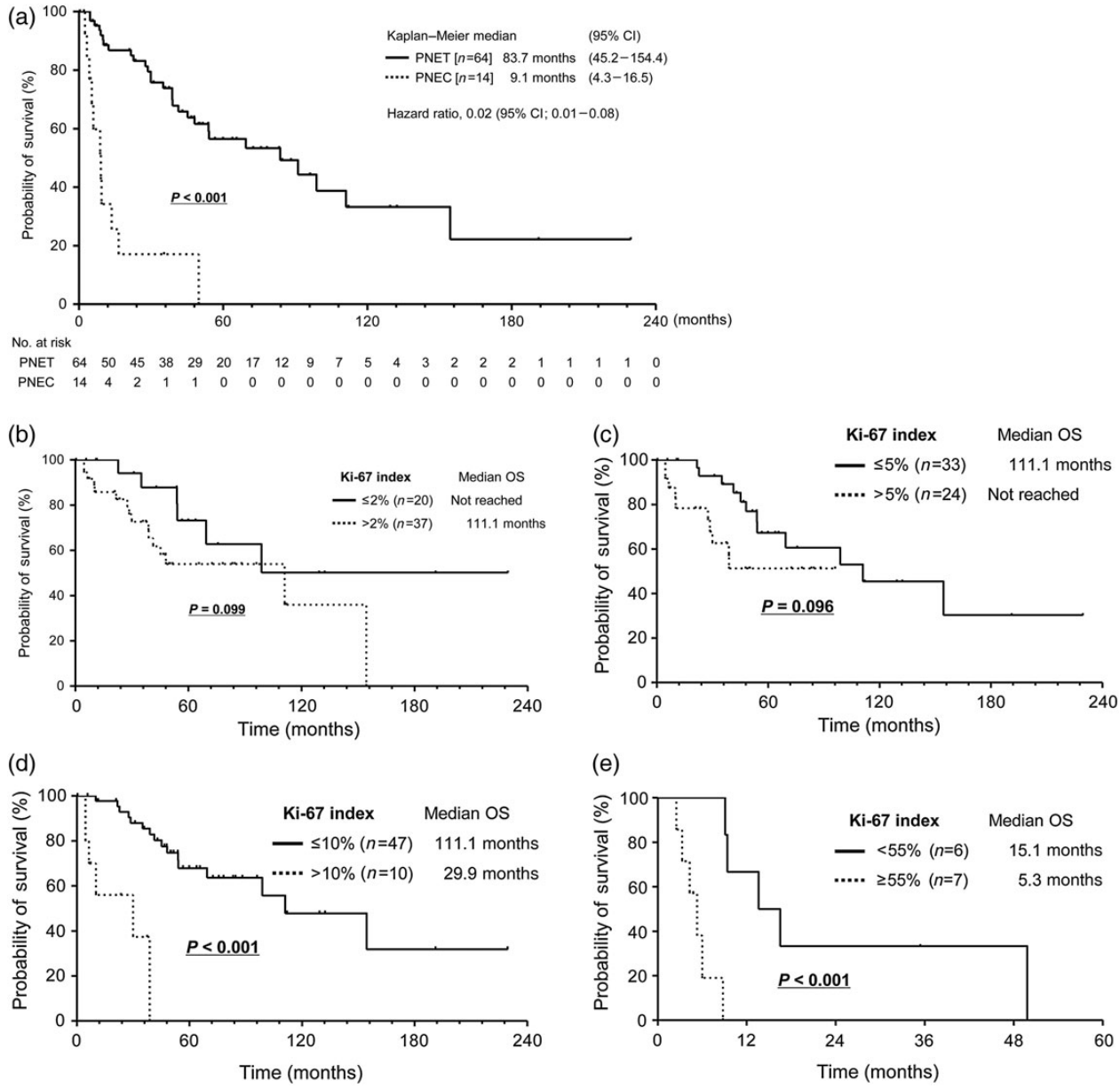

Figure 1. Kaplan–Meier analyses of overall survival. (a) Overall survival in patients with pancreatic neuroendocrine tumor (PNET) and pancreatic neuroendocrine carcinoma (PNEC). Survival comparison using the Ki-67 cut-off values of 2% (b), 5% (c) and 10% (d) in patients with PNET, and 55% in patients with PNEC (e).

$P = 0.096$) failed to show significance, a cut-off value of 10% (HR: 9.95, 95% CI: 3.01–32.97, $P < 0.001$) had a significant prognostic value in patients with PNET.

An analysis of 13 patients with PNEC using the recently reported cut-off value of 55% (47) showed a significant prognostic difference between patients with Ki-67 ≥ 55% and patients with Ki-67 between 21–54% (median: 5.3 months vs 15.1 months, HR: 19.2, $P < 0.001$) (Fig. 1e).

Univariate analysis

A univariate analysis performed with several clinicopathological factors, listed in Table 3, revealed that presence of bone metastases was a significant prognostic factor in patients with PNET (HR: 4.38, 95% CI: 1.42–11.29, $P = 0.013$) (Fig. 2a). In addition, patients treated after the advent of targeted therapies had significant better prognosis than those who terminated treatment before their implementation (HR: 0.07, 95% CI: 0.03–0.19, $P < 0.001$) (Fig. 2b). Other reported prognostic factors, such as age (27,48), functional status (15,19,26,48,49), diffuse hepatic metastases (16,27,41,50) and aggressive surgery for primary tumor and liver metastases (14,16,24,51,52) failed to show significance in our study population. With age, no significance was observed with other cut-off points, such as 45, 50 or 60 years (data not shown).

Multivariate analysis

A multivariate analysis in patients with PNET showed that a Ki-67 index of ≥10% (HR: 38.8, 95% CI: 8.42–226.62, $P < 0.001$) and the presence of bone metastases (HR: 5.66, 95% CI: 1.10–24.00, $P =$

Table 3. Univariate analysis of prognostic factors for pancreatic neuroendocrine tumors

Variable	*n*	Median survival, months (95% CI)	Survival rate (%)			Hazard ratio (95% CI)	*P* value
			3-year	5-year	10-year		
Age (years old)							0.577
≤65	16	91.1 (48.1–ND)	80	60	41	1.0 (reference)	
>65	48	53.9 (21.9–98.8)	54	45	15	1.73 (0.74–3.73)	
Gender							0.930
Male	33	83.7 (29.9–ND)	68	53	34	1.03 (0.50–2.19)	
Female	31	91.1 (38.9–154.4)	81	63	33	1.0 (reference)	
MEN type1							0.347
Present	11	111.1 (21.6–ND)	80	69	34	0.64 (0.21–1.57)	
Absent	53	69.4 (38.9–154.4)	73	53	36	1.0 (reference)	
Ki-67 index (%)							<0.001
≤10	47	111.1 (69.4–ND)	85	68	48	1.0 (reference)	
>10	10	29.9 (4.6–38.8)	37	0	0	9.95 (3.01–32.97)	
Hormonal production							0.148
Yes	20	48.1 (27.6–111.1)	62	34	25	1.74 (0.81–3.63)	
No	44	91.1 (69.4–NA)	79	70	36	1.0 (reference)	
Previous curative resection[a]							0.094
Yes	29	98.8 (53.9–ND)	80	63	47	0.53 (0.23–1.11)	
No	35	69.4 (29.9–111.1)	68	50	23	1.0 (reference)	
No. of disease sites							0.073
1–2	41	91.1 (53.9–ND)	84	62	38	1.0 (reference)	
≥3	23	41.3 (12.3–154.4)	56	46	26	1.97 (0.94–4.10)	
Diffuse hepatic metastases (≥5 lesions)							0.935
Yes	45	91.1 (38.9–154.4)	75	57	36	0.97 (0.45–2.25)	
No	19	83.7 (27.6–ND)	71	57	30	1.0 (reference)	
Lymph nodes metastases							0.676
Yes	35	83.7 (38.8–154.4)	72	58	32	1.17 (0.56–2.57)	
No	29	98.8 (38.8–ND)	76	53	36	1.0 (reference)	
Bone metastases							0.013
Yes	8	22.7 (8.5–ND)	19	0	0	4.38 (1.42–11.29)	
No	56	91.1 (53.9–154.4)	80	61	36	1.0 (reference)	
Aggressive surgery[b]							0.744
Yes	17	111.1 (27.6–ND)	76	63	35	0.87 (0.35–1.93)	
No	47	83.7 (45.2–154.4)	75	56	34	1.0 (reference)	
Treatment timing							<0.001
Before targeted therapies	12	22.2 (8.5–38.8)	25	0	0	1.0 (reference)	
After targeted therapies	52	98.8 (69.4–ND)	87	72	43	0.07 (0.03–0.19)	

CI, confidence interval; ND, not detected.

[a]Included curative resection for primary and/or metastatic sites before the diagnosis of unresectable.

[b]Non-curative resection for primary site and/or metastatic sites after the diagnosis of unresectable.

0.039) were independent predictors for poor prognosis. Treatment after the approval of targeted therapies correlated significantly with better prognosis (HR: 0.02, 95% CI: 0.00–0.11, $P < 0.001$) (Table 4). Although no significance was observed, patients with functional tumors seemed to have poorer prognosis than those with non-functioning tumors (HR: 2.68, 95% CI: 0.98–7.62, $P = 0.054$).

Discussion

Although numerous studies have been performed, the long-term outcomes and prognostic factors in patients with NEN remain unclear and variable in different Western series, mainly due to their rarity and heterogeneity. Moreover, little is known about Japanese patients, with advanced stage, and NEN of pancreatic origin (PNEN).

For the first time, our study showed that the median survival time and 5-year survival rate of Japanese patients with advanced PNET were 83.7 months and 56%, respectively. Our results are consistent with several reports from Western countries focusing on the outcome of advanced PNET (16–20,22), but differ from other studies (4,5,12–15,23–26,44,48). It is difficult to explain the exact reason for these discrepancies, but these may partially stem from differences in study populations, study period, therapeutic strategies and ethnicity.

Ki-67 index is generally considered an important prognostic predictor of NET (30). Although the WHO classification (28) proposes a cut-off value of 2%, which has been validated in some studies (17,23,29–32), other studies showed that a cut-off of 5% (18,25,33–36) or 10% (37–39) have a better prognostic value in separating G1 and G2 tumors. In 141 patients with metastatic PNET, Khan et al. (18) reported that a threshold of 5% had stronger prognostic value than 2%. Two studies by Panzuto et al. (15,35) included more than a hundred patients with metastatic PNET and also demonstrated the prognostic value of a 5% cut-off. However, small bowel NET (15) and non-metastatic PNET (35) were included in these latter analyses. Strosberg et al. (16) also reported that the tumor histological grade was a strong prognostic factor in 53 patients with metastatic PNET. The median survival was 86 and 22 months among patients with well and moderately differentiated tumors, respectively. Unfortunately, the Ki-67 value was not analyzed in this study. Thus, there is

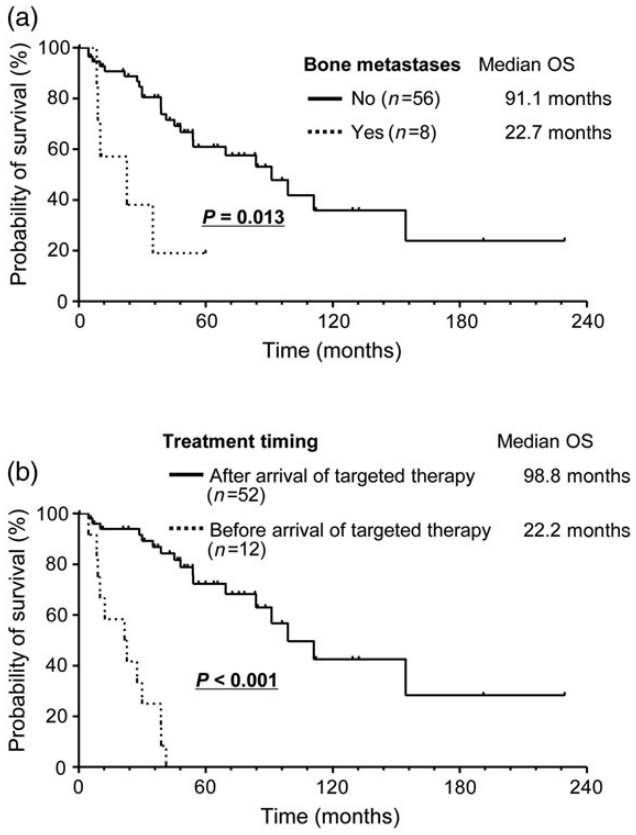

Figure 2. Kaplan–Meier analyses of different prognostic factors. Overall survival in patients with advanced PNET according to bone metastases (a) and treatment timing (b).

Table 4. Multivariate analysis of prognostic factors of pancreatic neuroendocrine tumors

Variable	Hazard ratio	(95% CI)	*P* value
Ki-67 index (>10 vs ≤10%)	38.8	(8.42–226.62)	<0.001
Previous curative resection (yes vs no)	1.29	(0.40–4.63)	0.673
No. of disease sites (≥3 vs 1–2)	1.12	(0.32–4.05)	0.863
Bone metastases (yes vs no)	5.66	(1.10–24.00)	0.039
Hormonal production (yes vs no)	2.68	(0.98–7.62)	0.054
Treatment timing (after vs before targeted therapies)	0.02	(0.00–0.11)	<0.001

still significant controversy of the grading cutoffs in different groups of patients with advanced PNET/NET. Our current study revealed that a Ki-67 index of 10%, but not 2 or 5%, was a strong prognostic and predictive cut-off value in patients with advanced PNET. This cut-off may be helpful, especially in Japanese patients with advanced PNET, but still needs to be validated for NET with other origins and stages.

Though other prognostic factors of NET have investigated in many studies, there are still a number of areas of debate. From our study, a multivariate analysis confirmed bone metastases as a significant predictor of poor prognosis. Similar results are reported in several studies (41,42,51). This result may some part result from the lack of effective therapeutic agents with bone metastasis, such as transarterial chemoembolization and radiofrequency ablation against liver metastasis. In addition, considering that the number of disease sites (≥3) did not affect survival in the same population, patients with bone metastases might be in the most advanced stage, regardless of the primary site. Similarly, previous curative resection did not affect the outcome in our study. This result also suggested that long-term outcome of advanced PNET is affected by whether the unresectable metastases are controlled by multimodal therapies, and not by whether the metastases are synchronic or metachronic. In contrast, several reported factors, such as age (27,48) and diffuse or unresectable liver metastases (16,27,41,50) did not impact survival in our study. Functioning tumors seemed to have poorer prognosis than non-functioning tumors in our study, but the prognostic effect of tumor functionality is still controversial (15,19,26,48,49). One possible reason for these discrepancies is that the majority of previous studies have included various stages of disease and primary sites. The long-term outcomes of NET are known to differ greatly according to these factors, with poor prognoses in patients with pancreas origin (4–6,15,27,29,38,42) and metastatic disease (12–14,19,26,29,30,33,38,53,54). Thus, prognostic factors of advanced PNET should be analyzed separately.

With respect to recent advances in the treatment of advanced PNET, Modlin et al (5) reported that 5-year survival rates of distant PNET in the Surveillance, Epidemiology, and End Results (SEER) database were 24.1% within the early subset (1973–91) and 40.9% within the late subset (1992–99). Similar results were reported by Yao et al. (4), including patients with metastatic PNET in the SEER database diagnosed from 1988 to 2004. In their study, the median survival and 5-year survival rates were 27 months and 27%, respectively. As a result of limited treatment options during the study period, prognosis of advanced PNET did not improve dramatically.

Recently, two targeted therapeutic agents, everolimus (8) and sunitinib (9), have demonstrated significant clinical benefits in Phase III trials involving patients with advanced PNET. Although the efficacy of these agents in Japanese patients has been reported for a small number of patients (10,11), our current study provides support for the first time that the arrival of these agents has significantly prolonged survival of Japanese patients with advanced PNET. As patients with advanced PNET are usually treated with multimodal approach encompassing chemotherapy, radiotherapy, liver-directed therapy and surgical resection (1,2), it is difficult to evaluate the prognostic efficacy of individual treatment modalities. In fact, aggressive resection of primary or metastatic sites, reported to be effective in several studies (14,16,24,51,52), failed to show significance in our study. One possible reason for this discrepancy is that most of the debulking surgery was performed at the early time of our study period, so that they could not receive other effective treatment, especially with targeted therapy. In addition, because the treatment strategy of aggressive surgery for primary and metastatic site is different, and the debulking rates were not available in most patients, our result might not reflect the true efficacy of aggressive surgery against metastatic PNET. Similarly, the prognostic efficacy of other treatment options could not be analyzed in our study due to the lack of detailed information and therapeutic strategies. However, despite these limitations, considering that the poor prognosis of patients treated before the advent of targeted therapy (median: 22.2 months, 5-year survival rate: 27%) was similar to previous reports, mentioned above (4, 5), our results support the conclusion that both everolimus and sunitinib could be contributed to the prolongation of survival in Japanese patients with advanced PNET. Moreover, these results also suggest that we come to be able to manage and control liver metastases well using targeted therapeutic agents. Thus, the arrival of these agents could impact several reported

prognostic factors such as liver metastases (16,27,41,50). Further study may be required to clarify this point.

Patients with NEC are known to have poorer prognosis than patients with NET (18,19,22,30,33,35,44), but little is known about Japanese patients. From our study, median survival was only 9.1 months, with a 1-year survival rate of 34%. Similar result was reported from Yamaguchi et al. (55), including 35 patients with PNEC. It showed that that median OS and 1-year survival rate were 8.5 months and 34%, respectively. One certain reason for these disappointing results is the lack of high-level evidence and effective therapeutic regimens for these populations. A recent large retrospective study, the NORDIC NEC study (47), examined 252 patients with gastrointestinal NEC. It showed that patients with Ki-67 < 55% had longer survival (14 months vs 10 months, $P < 0.001$), but a lower response rate to first-line chemotherapy (15 vs 42%, $P < 0.001$) than patients with Ki-67 ≥ 55%. These results were supported by other Western study (15). The results from our study show this cut-off value has an important prognostic effect on Japanese patients with G3 tumors (NEC), and it likely will prove to have an important role in selecting treatment options for patients with advanced PNEC, similar to shown in recent Western studies (15,47). Interestingly, there were no prognostic significance between patients with Ki-67 between 11–20 and patients with Ki-67 between 21–54 (HR: 1.07, $P = 0.921$). This result suggests that Ki-67 value separating G2 tumor and NEC should also be validated.

There are several limitations in our study. First, screening for bone metastases was performed using CT and/or MRI that were reported to have lower detection power in PNET (51). Although the frequency of bone metastases in our study population (10%) was consistent with previous report from Kavecansky et al (51), the prevalence rate of bone metastases in our study might have been underestimated. Second is the accuracy of Ki-67 index. Intratumoral heterogeneity of Ki-67 index in PNET are well known, and previous report from Hasegawa et al (56) have raised attention when calculating Ki-67 index with small biopsy specimens, <2000 tumor cells, that causes the discrepancy between resected specimens and biopsy specimens. It should be taken into consideration that Ki-67 index of 26 patients (37%) were evaluated from biopsy specimens in the present study. Other limitations of our study, such as the study design, number of patients and limited treatment data, did not allow a complete examination of the rarity and heterogeneity of NET. Further study is required to elucidate the differences in the long-term outcome and prognostic factors of advanced PNET between Japan and Western nations. However, our findings might be invaluable in further studies, which are required to establish higher-level evidence in this area, especially for those focusing on Japanese patients with advanced PNET.

In conclusion, we have elucidated the long-term outcomes in Japanese patients with advanced PNEN. With respect to advanced PNET, a Ki-67 threshold of 10% and bone metastases were independent prognostic factors. Moreover, the arrival of targeted therapeutic agents significantly prolonged survival.

Authors' contributions

L.L., H. I. and T.I conceived and designed the study. L.L., H.I., N.F. and T.I. acquired the data. L.L., H.I., M. H., K.K. and T.I. analyzed and interpreted the data. L.L., H.I., Y.O., R.T.J. and T.I drafted the manuscript. L.L., H.I., Y.O., R.T.J. and T.I. critically reviewed the manuscript.

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Conflict of interest statement

None declared.

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