Pancreatology 22 (2022) 123–129

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Preoperative risk stratification of lymph node metastasis for non-functional pancreatic neuroendocrine neoplasm: An international dual-institutional study

Yosuke Kasai [a, b, c], Toshihiko Masui [a, *], Eric K. Nakakura [b, c], Kenzo Nakano [a], Asahi Sato [a], Yuichiro Uchida [a], Akitada Yogo [a], Kazuyuki Nagai [a], Takayuki Anazawa [a], Thomas A. Hope [c, d], Grace E. Kim [c, e], Julia Whitman [c], Bryan K. Le [c], Kyoichi Takaori [a], Emily K. Bergsland [c, f], Etsuro Hatano [a], Shinji Uemoto [a]

[a] Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[b] Department of Surgery, University of California, San Francisco, USA
[c] UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA
[d] Department of Radiology and Biomedical Imaging, University of California, San Francisco, USA
[e] Department of Pathology, University of California, San Francisco, USA
[f] Department of Medicine, University of California, San Francisco, USA

ARTICLE INFO

Article history:
Received 13 March 2021
Received in revised form
29 September 2021
Accepted 25 October 2021
Available online 28 October 2021

Keywords:
Lymphadenectomy
Malignant potential
Resection

ABSTRACT

Background: /Objectives: Although the presence of lymph node metastasis (LNM) defines malignant potential, preoperative prediction of LNM has not been established for non-functional pancreatic neuroendocrine neoplasm (NF-PNEN). We sought to develop a prediction system using only preoperatively available factors that would stratify the risk of LNM for NF-PNEN.

Methods: We retrospectively reviewed patients who underwent R0/1 resection of NF-PNEN at Kyoto University (2007–2019) and the University of California, San Francisco (2010–2019). Risk stratification of LNM was developed using preoperative factors by the logistic regression analysis. Long-term outcomes were compared across the risk groups.

Results: A total of 131 patients were included in this study. Lymph nodes were pathologically examined in 116 patients, 23 (20%) of whom had LNM. Radiological tumor size [1.5–3.5 cm (odds ratio: 13.5, 95% confidence interval: 1.77–398) and >3.5 cm (72.4, 9.06–2257) against ≤1.5 cm], <50% cystic component (8.46 × 10^6, 1.68 × 10^106-), and dilatation of main pancreatic duct ≥5 mm (31.2, 3.94–702) were independently associated with LNM. When patients were classified as the low-risk (43 patients), intermediate-risk (44 patients), and high-risk groups (29 patients), proportions of LNM differed significantly across the groups (0%, 14%, and 59%, respectively). Recurrence-free survival (RFS) of the low- and intermediate-risk groups were significantly better than that of the high-risk group (5-year RFS rates of 92.2%, 85.4%, and 47.1%, respectively).

Conclusions: The prediction system using preoperative radiological factors stratifies the risk of LNM for NF-PNEN. This stratification helps to predict malignant potential and determine the surgical procedure and necessity of regional lymphadenectomy.

1. Introduction

Neuroendocrine neoplasm (NEN) is a rare malignancy, but the incidence has increased six-fold over the past four decades [1]. The pancreas is the fourth most common primary site of NENs, following the lung, small intestine, and rectum [1]. Although the prognosis of pancreatic neuroendocrine neoplasm (PNEN) is much better than that of pancreatic ductal adenocarcinoma, long-term survival is relatively unfavorable compared to the other NENs [1–3].

* Corresponding author. Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Shogoin, Kawahara-cho, Sakyo-ku, Kyoto, 606TEL, Japan.
E-mail address: tmasui@kuhp.kyoto-u.ac.jp (T. Masui).

https://doi.org/10.1016/j.pan.2021.10.005

Abbreviations

CART	classification and regression trees
CBD	common bile duct
CT	computed tomography
EUS	endoscopic ultrasound
FNA	fine needle aspiration
LNM	lymph node metastasis
LVI	lymphovascular invasion
MPD	main pancreatic duct
MRI	magnetic resonance imaging
NEN	neuroendocrine neoplasm
NF-PNEN	non-functional pancreatic neuroendocrine neoplasm
OS	overall survival
PET	positron emission tomography
PNEN	pancreatic neuroendocrine neoplasm
RFS	recurrence-free survival
ROC	receiver operating characteristic
UCSF	University of California, San Francisco

PNENs are classified into two types: hormone-producing functional PNEN and non-functional PNEN (NF-PNEN), the latter accounting for 65–85% of PNENs [4,5]. Although functional PNEN is generally recommended for resection regardless of the tumor size to control hormonal symptoms, the surgical indication for small NF-PNEN ≤2 cm has been controversial, because most of them have indolent characteristics [6,7]. Since the presence of lymph node metastasis (LNM) defines a malignant PNEN, pancreatic resection with regional lymphadenectomy is recommended for patients with suspicious LNM even if the primary tumor is small and non-functional [6,7]. Although several factors have been associated with LNM, including tumor size, site of primary tumor, calcification, cystic component, main pancreatic duct (MPD) involvement, and Ki-67 index [8–16], there are few comprehensive prediction systems of LNM because PNEN is rare and large-scale studies are lacking [9,14]. We and others have shown that Ki-67 index is highly associated with LNM [14,16]. However, the accurate Ki-67 index is usually unavailable preoperatively, because Ki-67 index on specimens from preoperative endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) is often lower than that on surgical specimens, and the grade is underestimated in 20–30% of cases due to intratumor heterogeneity [17,18]. Therefore, prediction models using Ki-67 index might not be best for deciding resection versus observation or the necessity of regional lymphadenectomy.

In this international dual-institutional study, we sought to develop a prediction system using only preoperatively available factors that would stratify the risk of LNM and malignant potential of NF-PNEN.

2. Methods

Patients. This study was conducted at Kyoto University and the University of California, San Francisco (UCSF). Patients who underwent R0/1 resection of primary NF-PNEN between 2007 and 2019 at Kyoto University and between 2010 and 2019 at UCSF were retrospectively reviewed. Patients with known germline mutations (including *MEN1* and *VHL* genes), distant metastasis, coincidence of pancreatic ductal adenocarcinoma, or missing Ki-67 information were excluded. Data were collected from medical records, operative reports, and pathological reports. This study was conducted in accordance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, and Health Insurance Portability and Accountability Act in the USA. The study protocol was approved by the institutional review boards of both institutions.

Preoperative radiological findings. Tumor size, early enhancement, cystic component <50%, calcification, MPD dilatation ≥5 mm, and lymphadenopathy were evaluated on preoperative imaging as possible risk factors of N1 (=LNM) according to the previous studies [8,10–13,15,19]. All patients received preoperative computed tomography (CT) and/or magnetic resonance imaging (MRI). The findings of EUS were referred when the tumors were too small to be detected on CT or MRI. Early enhancement was evaluated on the arterial phase of three-phase dynamic CT or MRI. Cystic component was differentiated from necrosis by a well-circumscribed, regular shape and homogenous density/intensity without enhancement. Calcification was evaluated on non-contrast CT. MPD dilatation was evaluated on CT and/or MRI. Radiological lymphadenopathy was defined as nodes >10 mm in the short axis [20].

Surgical procedures. Surgical procedure was determined based on the site of the primary tumor, size, and MPD involvement. Regional lymphadenectomy was generally performed concurrently with pancreaticoduodenectomy, or distal, total, or central pancreatectomy. Tumor enucleation was done for small lesions that did not involve the MPD.

Postoperative follow-up. Patients had follow-up every 3–6 months with contrast-enhanced computed tomography or magnetic resonance imaging. Recurrence was recorded when any radiological modalities first detected PNEN-related malignant diseases. Patients were censored for follow-up of recurrence and survival at the end of 2019.

Statistical analysis. Categorical variables were expressed as the number and the percentage, and compared using the chi-squared test. Continuous variables were expressed as the median and interquartile range, and compared using the Wilcoxon test. To construct a risk stratification for N1, patients whose nodes were pathologically examined were included in the analysis (patients with NX were excluded). The classification and regression trees (CART) method was used to classify tumor size for the outcome of N1. In brief, patients are classified to two groups (called “nodes”) based on the value of a covariate which best discriminate an outcome (N1 in this study), and then each node is classified in turn if feasible [21]. Logistic regression analysis was performed for the outcome of N1 using preoperative factors. Patients were classified into risk groups according to the logit for N1 using the CART method. Discriminatory power of the risk stratification for N1 was evaluated using receiver operating characteristic (ROC) analysis. A 10-fold cross validation was performed using the identified risk factors. Pathological findings and long-term outcomes were analyzed in the entire cohort (including patients with NX). Recurrence-free survival (RFS) and overall survival (OS) were compared using the log-rank test. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using JMP software version 10 (SAS Institute, Cary, NC).

3. Results

Patient and tumor characteristics. A total of 131 patients (56 from Kyoto University and 75 from UCSF) were included in this study (Table 1). Race differed significantly between the institutions because all patients from Kyoto University were Asian. Tumor size was smaller and tumor enucleation was more frequent at Kyoto University than at UCSF. Accordingly, proportion of NX was higher at Kyoto University than at UCSF. When patients with NX were excluded, 23 of 116 patients (20%) had N1 and the proportions of N1

Table 1
Patient and tumor characteristics.

Variables	Total (n = 131)	Kyoto cohort (n = 56)	UCSF cohort (n = 75)	*P*-value
Age	60 (52–65)	61 (54–65)	59 (48–66)	0.543
Sex female	62 (47%)	30 (54%)	32 (43%)	0.216
Race				<0.001
Asian	65 (50%)	56 (100%)	9 (12%)	
White	50 (38%)	0 (0%)	50 (67%)	
Hispanic	8 (6%)	0 (0%)	8 (11%)	
Black	5 (4%)	0 (0%)	5 (7%)	
Not specified	3 (2%)	0 (0%)	3 (4%)	
Radiological findings				
Site of primary				0.032
Head	45 (34%)	25 (45%)	20 (27%)	
Body/Tail	86 (66%)	31 (55%)	55 (73%)	
Tumor size (cm)	2.0 (1.3–3.2)	1.7 (1.0–2.5)	2.4 (1.5–3.6)	0.007
Early enhancement	80/117 (68%)	42/56 (75%)	38/61 (62%)	0.138
Cystic component <50%	121 (92%)	54 (96%)	67 (89%)	0.115
Calcification	25 (19%)	13 (23%)	12 (16%)	0.318
Main pancreatic duct ≥5 mm	9 (7%)	3 (5%)	6 (8%)	0.549
Surgical procedure				<0.001
Pancreaticoduodenectomy	41 (31%)	22 (39%)	19 (25%)	
Distal pancreatectomy	74 (56%)	21 (38%)	53 (71%)	
Central pancreatectomy	6 (5%)	5 (9%)	1 (1%)	
Total pancreatectomy	2 (2%)	1 (2%)	1 (1%)	
Tumor enucleation	8 (6%)	7 (13%)	1 (1%)	
Pathological findings				
Primary tumor				0.445
T1-2	106 (81%)	47 (84%)	59 (79%)	
T3-4	25 (19%)	9 (16%)	16 (21%)	
Lymph node metastasis				<0.001
N0	93 (71%)	34 (61%)	59 (79%)	
N1	23 (18%)	8 (14%)	15 (20%)	
NX	15 (11%)	14 (25%)	1 (1%)	
Number of nodes examined[a]	13 (6–18)	7 (3–12)	16 (12–19)	<0.001
Lymphovascular invasion	27/123 (22%)	11/48 (23%)	16/75 (21%)	0.836
Perineural invasion	21/116 (18%)	7/41 (17%)	14/75 (19%)	0.831
Necrosis	15/93 (16%)	5/18 (28%)	10/75 (13%)	0.157
Positive surgical margin	15 (11%)	7 (13%)	8 (11%)	0.745
Ki-67 index (%)	2.0 (1.0–4.4)	1.2 (1.0–3.9)	2.4 (1.0–4.9)	0.057
WHO2017 grade				0.647
G1	81 (62%)	37 (66%)	44 (59%)	
G2	48 (37%)	18 (32%)	30 (40%)	
G3	2 (2%)	1 (2%)	1 (1%)	

[a] The values are of patients excluding NX.

were comparable between the institutions (19% for Kyoto University and 20% for UCSF). All tumors, including 2 G3 tumors, were well-differentiated. No patients with poorly-differentiated neuroendocrine carcinoma were included in this study.

Risk stratification of N1. Among 116 patients (excluding those with NX), tumor size, <50% cystic component, calcification, dilatation of MPD ≥5 mm, and lymphadenopathy were significantly associated with N1 (Table S1). In multivariate analysis, tumor size (1.5–3.5 cm and >3.5 cm against ≤1.5 cm), <50% cystic component, and dilatation of MPD ≥5 mm were independent risk factors for N1 (Table 2). Patients were classified into the low-risk (43 patients), intermediate-risk (44 patients), and high-risk groups (29 patients) according to the logit for N1 using the three radiological parameters (Fig. 1A). The low risk represents ≤1.5 cm without MPD dilatation, or ≥50% cystic component of any size; the intermediate risk represents 1.5–3.5 cm with <50% cystic component and without MPD dilatation; and the high risk represents >3.5 cm with <50% cystic component, or MPD dilatation of any size (Fig. 1B). Proportions of N1 differed significantly across the risk groups (0%, 14%, and 59%, respectively, Fig. 2A). Although tumor size also moderately discriminated the risk of N1 (Fig. 2B), the risk stratification had better discriminatory power than tumor size alone (the area under the curve of ROC of 0.865 and 0.778, respectively, Fig. 2C). The similar trend in the proportions of N1 by the risk stratification was observed for each of the Kyoto and UCSF cohort (Fig. 3A and B). A 10-fold cross validation showed that the logit for N1 using the three radiological parameters were highly concordant with the original one (Fig. S1). Radiological lymphadenopathy was highly specific, but not sensitive for N1 (specificity of 96% and sensitivity of 35%, Table S1). Among patients without lymphadenopathy, the risk stratification discriminated the risk of N1 appropriately (Fig. S2A). Also, among patients with lymphadenopathy, the similar trend was observed, though the differences did not reach statistical significance (Fig. S2B).

Pathological findings and long-term outcomes. Ki-67 index on the resected specimens differed significantly across the risk groups [median 1.0% (0.8–2.0), 2.0% (1.0–3.5), and 4.9% (3.0–10.0), Fig. 4A]. Accordingly, the proportions of G2-3 differed (18%, 32%, and 81%, Fig. 4B), though the difference between the low- and intermediate-risk groups was not statistically significant because Ki-67 index ranged within the G1 category (<3%) in most cases of the two groups. Lymphovascular invasion (LVI) also differed significantly across the risk groups (2%, 15%, and 61%, Fig. 4C). No patients received adjuvant therapy after surgery before recurrence. RFS for the low- and intermediate-risk groups were comparable and significantly better than that for the high-risk group (5-year RFS rates of 92.2%, 85.4%, and 47.1%, respectively, Fig. 5A). During median follow-up of 42 months, OS were comparable across the

Table 2
Logistic regression analysis for N1 among 116 patients excluding those with NX.

Variables		Univariate analysis			Multivariate analysis		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value
Institution	Kyoto	ref					
	UCSF	1.08	0.42–2.93	0.874			
Age ≥60		1.22	0.49–3.12	0.673			
Female		0.55	0.20–1.38	0.203			
Race	White	ref					
	Asian	0.84	0.32–2.22	0.727			
	Others	0.49	0.07–2.15	0.369			
Primary tumor in the head		1.29	0.49–3.27	0.603			
Tumor size (cm)	≤1.5	ref			ref		
	1.5–3.5	7.36	1.29–139	0.021	13.5	1.77–398	0.008
	>3.5	36.0	6.25–687	<0.001	72.4	9.06–2257	<0.001
Early enhancement		0.75	0.28–2.11	0.582			
Cystic component <50%		8.10 × 10^6	2.63 × 10^16-	0.041	8.46 × 10^6	1.68 × 10^106-	0.039
Calcification		3.30	1.19–9.02	0.023	–	–	–
Main pancreatic duct ≥5 mm		16.1	3.39–116	<0.001	31.2	3.94–702	<0.001

CI: confidence interval, OR: odds ratio.

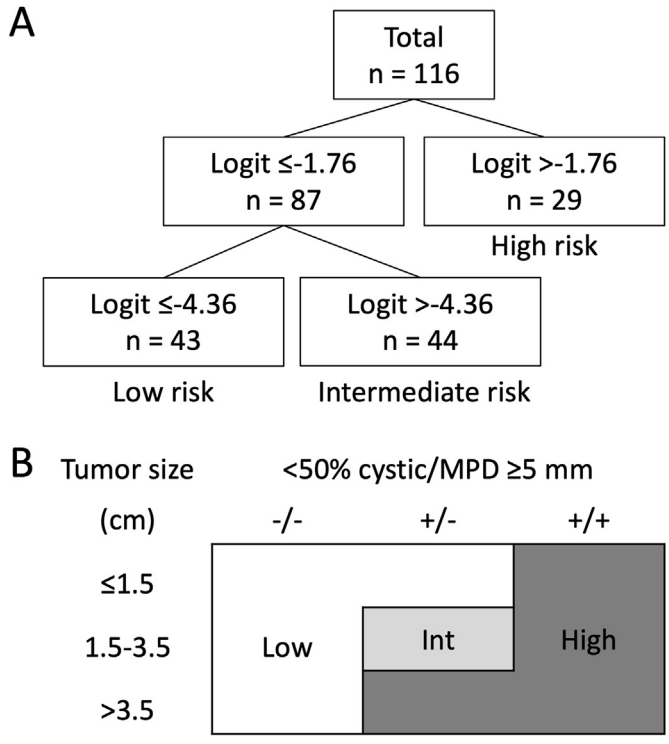

Fig. 1. Risk stratification of N1. (**A**) The classification and regression trees (CART) method classified patients into three groups according to the logit for N1. Logit = −20.31 + (0, if ≤ 1.5 cm; 2.60, if 1.5–3.5 cm; 4.28, if > 3.5 cm) + (15.95, if <50% cystic; 0, otherwise) + (3.44, if MPD ≥5 mm; 0, otherwise). (**B**) A scheme of the risk groups. MPD: main pancreatic duct.

groups (5-year OS rates of 90.7%, 97.1%, and 87.9%, respectively, Fig. 5B)

Selection of tumor enucleation. Tumor enucleation was performed in 8 patients (6%, Table S2). The tumors that were enucleated were located either in the head (4 patients, 50%) or the body (4 patients, 50%), and none were located in the tail (Fig. S3). Five of them (63%) were exophytic from the surface of the pancreas. Most were ≥2 mm away from the MPD and common bile duct (CBD), except for one tumor which abutted on the MPD and CBD though no MPD or CBD dilatation was observed. Seven of them (88%) were <2 cm. None of them had possible radiological signs of malignancy, including disappearance of early enhancement, calcification, and lymphadenopathy. Given that tumors involving the MPD are not feasible for enucleation, the risk of N1 was evaluated among patients excluding those with MPD dilatation to seek for the appropriate indication of tumor enucleation (Table S3). In multivariate analysis, tumor size of >1.5 cm (not ≥2 cm) were independent risk factors for N1 among patients without MPD dilatation.

4. Discussion

In this international dual-institutional study, we sought to develop a prediction system that would stratify the risk of LNM and malignant potential of NF-PNEN. We found that LNM was predicted only by preoperative radiological factors. Although Ki-67 index/tumor grade is one of the most powerful prognosticators of patients with PNEN [5,22], we did not include Ki-67 index or tumor grade in this preoperative risk stratification, because preoperative grading by EUS-FNA is underestimated in 20–30% of cases due to intratumor heterogeneity [17,18]. In our cohort, tumor grade on EUS-FNA was underestimated in 21% of patients (Fig. S4A). The discriminatory power for N1 of grading by EUS-FNA was inferior to that of our risk stratification (Figs. S4B and C). Moreover, the risk stratification correlated well with pathological findings of Ki-67 index, tumor grade, and LVI on the resected specimens as well as LNM and prognosticated RFS. These findings suggest that our risk stratification represents the malignant potential of NF-PNEN.

Tumor size is one of the most common risk factors of PNEN. In a recent analysis of the National Cancer Database that included 2004 cases of NF-PNEN, resection was not superior to observation in OS for patients with tumors <1 cm, whereas resection was superior for patients with tumors 1–2 cm and >2 cm [23]. Consensus guidelines from the European Neuroendocrine Tumor Society accept initial observation for asymptomatic patients with low grade NF-PNEN <2 cm [6], whereas the threshold is ≤ 1 cm in the consensus guidelines from the North American Neuroendocrine Tumor Society [7]. In our study, the median tumor size was 2.0 cm. It would be an option to develop a risk stratification by this cutoff point. However, we sought to develop a better risk stratification than the existing ones. Based on the CART method, the size cutoff points of 1.5 cm and 3.5 cm best discriminated the risk of N1 as a univariate. The significance of the cutoff point at 1.5 cm has been shown in several studies [10,13,15,24], and this threshold could be another determinant for resection or observation or the necessity of lymphadenectomy.

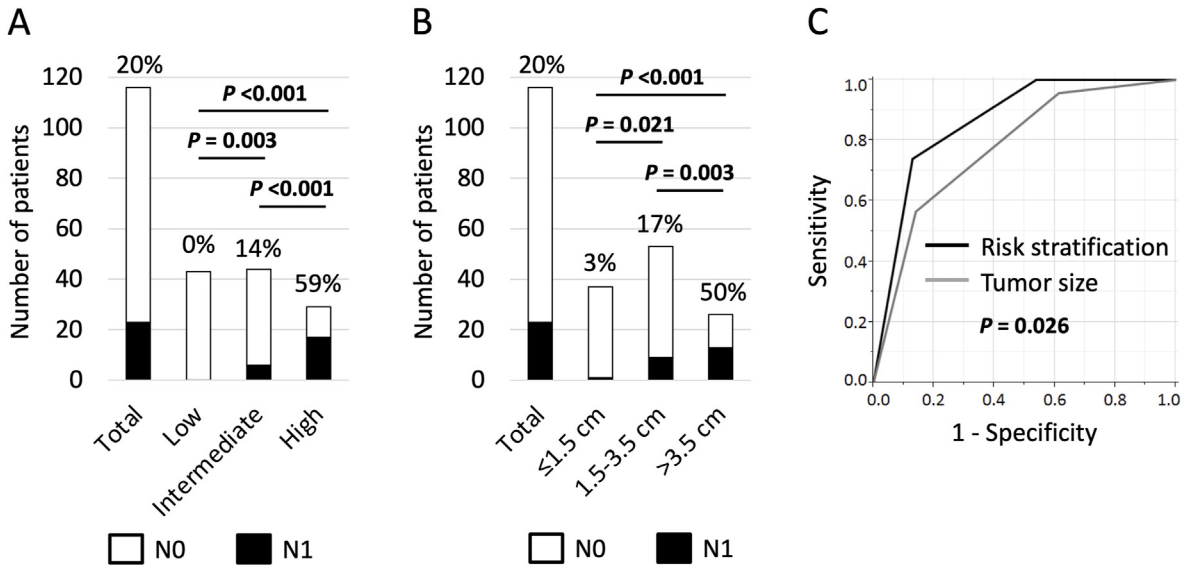

Fig. 2. Proportions of N1 were compared stratified by (**A**) the risk groups and **(B)** the tumor size using the chi-squared test. (**C**) Discriminatory power for N1 was compared between the risk stratification and tumor size (≤1.5 cm, 1.5–3.5 cm, and >3.5 cm). The area under the curve of receiver operating characteristic was 0.865 and 0.778, respectively, and the difference was 0.087 (95% confidence interval: 0.011–0.164).

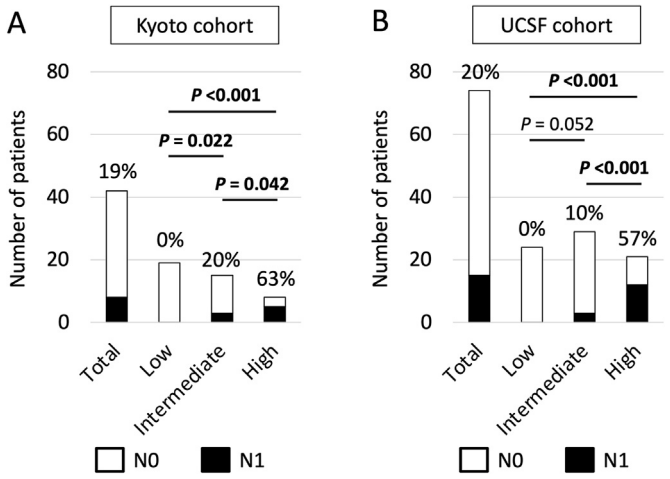

Fig. 3. Proportions of N1 stratified by the risk groups among **(A)** the Kyoto and **(B)** UCSF cohorts. Proportions of N1 were compared using the chi-squared test.

However, tumor size is not the sole factor that predicts malignant potential of PNEN. Indeed, around 25% of patients with NF-PNEN ≤2 cm were reported to have a Ki-67 index ≥3%, categorized to ≥ G2 [14,15]. Our prediction system, integrating the presence or absence of cystic component and dilatation of MPD as well as tumor size, was better than tumor size alone in predicting LNM (Fig. 2). Although the mechanism of cyst formation in PNEN is unknown, the favorable outcomes of patients with cystic PNEN have been well established. Cloyd et al. showed that 15 of 167 patients with NF-PNEN (9%) had ≥50% cystic component and none had LNM [12], which is fully compatible with our findings. A meta-analysis confirmed the benign behaviors of cystic PNEN compared to solid one, though 11% of patients with cystic PNEN did have LNM [25]. The relatively high incidence of LNM in the meta-analysis compared to zero incidence in Cloyd's and our studies might be due to confounding necrosis with cyst. Necrosis is an aggressive manifestation of PNEN and should be a distinct entity from cyst [26]. In our study, cystic component was radiologically defined as well-circumscribed, regular shape and homogenous density/intensity without enhancement to distinguish it from necrosis. In contrast, MPD involvement/dilatation has been shown as a malignant phenotype [13,19]. Nanno et al. showed that MPD involvement was associated with LNM, venous invasion, perineural invasion, Ki-67 index >2%, and short RFS [13]. They also showed an infiltrative growth pattern with fibrotic stroma of PNEN with MPD involvement, suggesting the specific aggressive biology. Our prediction system therefore combines well-established risk factors of PNEN. Since there were no patients with both ≥50% cystic component and MPD ≥5 mm in this study, it is inconclusive whether the condition with both radiological signs represented benign or malignancy if they could coexist. In such cases, however, we suggest not to underestimate the risk of malignant potential.

^{68}Ga DOTA TATE-positron emission tomography (PET)/CT is highly sensitive for detecting NENs [27]. In our cohort, there were 11 patients who had preoperative ^{68}Ga DOTA TATE-PET/CT. In 2 patients, ^{68}Ga DOTA TATE-avid lymph node apart from the primary tumor was detectable, and both patients actually had N1. In contrast, 2 other patients with N1 did not show focal uptake of ^{68}Ga DOTA TATE in the lymph nodes. Peritumoral lymph nodes may be indistinguishable from the primary tumor, which may pose a false negative. Due to the small number of patients, we are not able to conclude whether ^{68}Ga DOTA TATE-PET/CT is predictive of the malignant potential of PNEN.

Our prediction system could be practically applied to determining the surgical procedure and the necessity of regional lymphadenectomy. Given the low incidence of LNM, ≥G2, and LVI for the low-risk group, regional lymphadenectomy could be withheld and sampling for staging might be enough for low-risk patients. Tumor enucleation is an option for NF-PNEN to preserve pancreatic exocrine and endocrine functions under certain conditions, including head or body location, no obvious findings of MPD or CBD involvement, a small tumor, and no radiological lymphadenopathy. In the subgroup analysis of patients without MPD dilatation, tumor size of >1.5 cm, rather than ≥2 cm, was independent risk factors for N1 (Table S3). This finding suggests that tumor size of ≤1.5 cm without MPD involvement should be the indication of enucleation. In contrast, patients with MPD dilatation should undergo formal

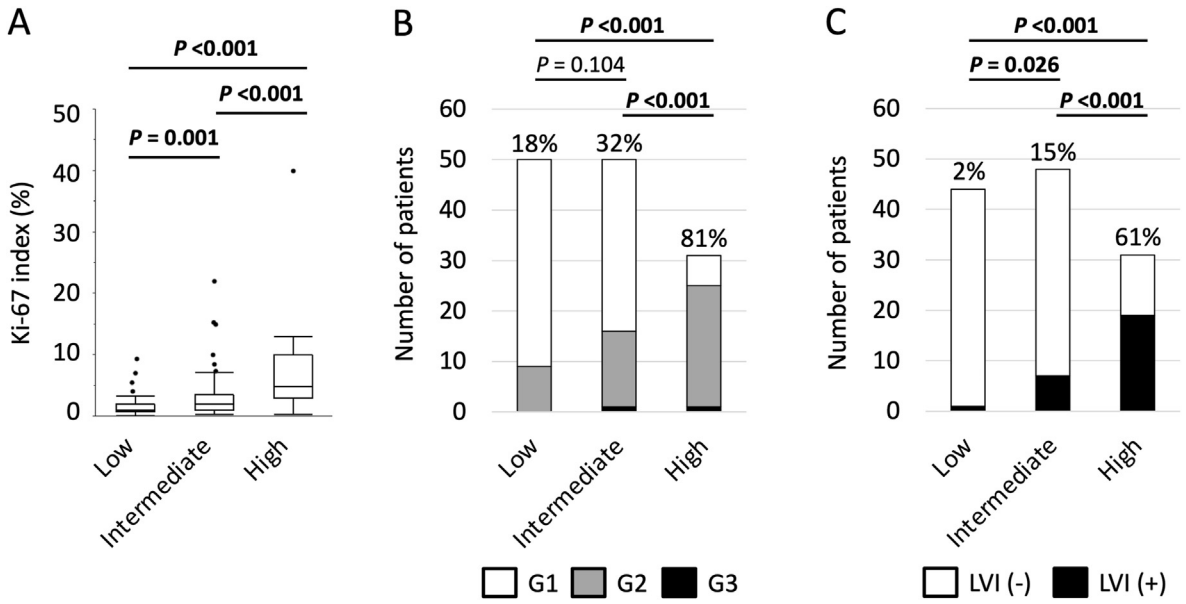

Fig. 4. Comparison of pathological findings across the risk groups **(A)** Ki-67 index was compared using the Wilcoxon test. **(B)** Proportions of G2-3 and **(C)** lymphovascular invasion (LVI) were compared using the chi-squared test.

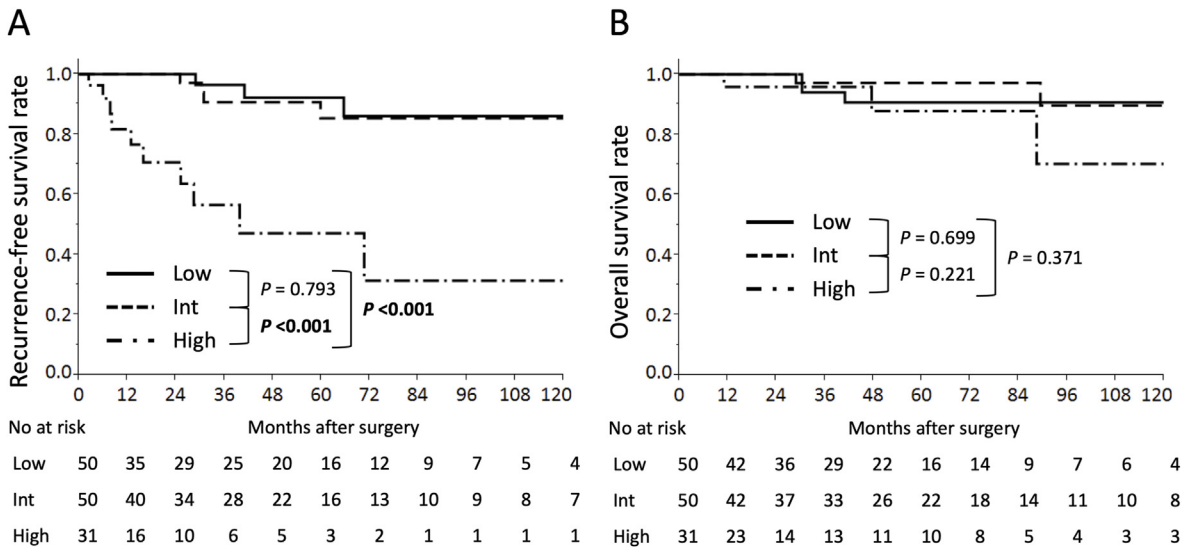

Fig. 5. (A) Recurrence-free survival and **(B)** overall survival were compared across the risk groups using the log-rank test.

pancreatectomy with regional lymphadenectomy even if they are small. Although our results do not permit us to conclude whether extended lymphadenectomy could improve the prognosis of the high-risk patients, it might be needed to achieve curative resection, given the high malignant potential.

Our risk stratification of N1 was prognostic for RFS, but not for OS. One reason for this should be the short follow-up period (median 42 months). In the survival analysis from the Surveillance, Epidemiology, and End Results Database, the median survival of patients with local and regional PNEN exceeded 90 months [1]. Therefore, longer follow-up would be needed to conclude the prognostic impact of our risk stratification on OS. Meanwhile, 9 out of 13 patients with recurrence in the liver received liver-directed therapy in our cohort, 5 of whom underwent resection of liver metastases. As we and others have described, complete or even debulking resection of neuroendocrine liver metastasis prolongs survival in select cases [28–31]. This might attenuate the potential difference of survival between high-risk and low to intermediate-risk groups despite their significant difference in the risk of recurrence.

Due to the rarity of PNEN, we collaboratively conducted an international dual-institutional study. Although patient and tumor characteristics differed significantly between the institutions in two countries, including race, the site of tumor (head vs body/tail), tumor size, and surgical procedure (the frequency of enucleation), the risk stratification was applicable to both institutional cohorts as shown in Fig. 3, which suggests that this system is universal. A 10-fold cross validation supplemented the validity of this system, though an external validation is desirable to further confirm our findings.

There are several limitations to this study. First, the scale of this study was modest compared to registry-based ones [23,32–35].

Nevertheless, our study has significance with respect to detailed evaluation of radiological imaging in contrast to such studies. Second, because the numbers of patients with ≥50% cystic component and those with dilatation of MPD ≥5 mm were small in this study, their predictive values for LNM might be overestimated. Third, due to the retrospective design of this study, the post-operative radiological modality was not unified, and this might possibly bias the detection of recurrence, especially for liver metastasis. Finally, the number of nodes examined was low for Kyoto cohort, which might lead to inaccurate staging. However, we generally performed standard regional lymphadenectomy concurrently with formal pancreatectomy, and we did not observe regional lymph node recurrence except for one patient who had 21 nodes dissected at the time of surgery.

In conclusion, the prediction system using preoperative radiological factors stratifies the risk of LNM. This system also predicted the malignant potential and prognosticated RFS. Therefore, this system helps in determining the surgical procedure and necessity of lymphadenectomy for NF-PNEN.

Acknowledgements

We thank Pamela Derish in the UCSF Department of Surgery for editing the manuscript. This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant number JP18K08677. Thomas A. Hope received commercial research funding from Clovis Oncology, Philips, Advanced Accelerator Applications. The other authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.10.005.

References

[1] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3(10):1335–42.
[2] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26(18):3063–72.
[3] Siegel RL, Miller KD, Jemal A. Cancer statistics. Ca - Cancer J Clin 2019;69(1):7–34.
[4] Ito T, Igarashi H, Nakamura K, Sasano H, Okusaka T, Takano K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol 2015;50(1):58–64.
[5] Pulvirenti A, Javed AA, Landoni L, Jamieson NB, Chou JF, Miotto M, et al. Multi-institutional development and external validation of a nomogram to predict recurrence after curative resection of pancreatic neuroendocrine tumors. Ann Surg 2019.
[6] Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 2016;103(2):153–71.
[7] Howe JR, Merchant NB, Conrad C, Keutgen XM, Hallet J, Drebin JA, et al. the North American neuroendocrine tumor society consensus paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas 2020;49(1):1–33.
[8] Poultsides GA, Huang LC, Chen Y, Visser BC, Pai RK, Jeffrey RB, et al. Pancreatic neuroendocrine tumors: radiographic calcifications correlate with grade and metastasis. Ann Surg Oncol 2012;19(7):2295–303.
[9] Partelli S, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A, et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). JAMA Surg 2013;148(10):932–9.
[10] Kishi Y, Shimada K, Nara S, Esaki M, Hiraoka N, Kosuge T. Basing treatment strategy for non-functional pancreatic neuroendocrine tumors on tumor size. Ann Surg Oncol 2014;21(9):2882–8.
[11] Postlewait LM, Ethun CG, Baptiste GG, Le N, McInnis MR, Cardona K, et al. Pancreatic neuroendocrine tumors: preoperative factors that predict lymph node metastases to guide operative strategy. J Surg Oncol 2016;114(4):440–5.
[12] Cloyd JM, Kopecky KE, Norton JA, Kunz PL, Fisher GA, Visser BC, et al. Neuroendocrine tumors of the pancreas: degree of cystic component predicts prognosis. Surgery 2016;160(3):708–13.
[13] Nanno Y, Matsumoto I, Zen Y, Otani K, Uemura J, Toyama H, et al. Pancreatic duct involvement in well-differentiated neuroendocrine tumors is an independent poor prognostic factor. Ann Surg Oncol 2017;24(4):1127–33.
[14] Lopez-Aguiar AG, Ethun CG, Zaidi MY, Rocha FG, Poultsides GA, Dillhoff M, et al. The conundrum of < 2-cm pancreatic neuroendocrine tumors: a preoperative risk score to predict lymph node metastases and guide surgical management. Surgery 2019;166(1):15–21.
[15] Dong DH, Zhang XF, Poultsides G, Rocha F, Weber S, Fields R, et al. Impact of tumor size and nodal status on recurrence of nonfunctional pancreatic neuroendocrine tumors ≤2cmafter curative resection :A multi -institutionalstudy of 392 cases. J Surg Oncol 2019;120(7):1071–9.
[16] Masui T, Sato A, Nakano K, Uchida Y, Yogo A, Anazawa T, et al. Predictive value of the Ki67 index for lymph node metastasis of small non-functioning pancreatic neuroendocrine neoplasms. Surg Today 2019;49(7):593–600.
[17] Boutsen L, Jouret-Mourin A, Borbath I, van Maanen A, Weynand B. Accuracy of pancreatic neuroendocrine tumour grading by endoscopic ultrasound-guided fine needle aspiration: analysis of a large cohort and perspectives for improvement. Neuroendocrinology 2018;106(2):158–66.
[18] Hasegawa T, Yamao K, Hijioka S, Bhatia V, Mizuno N, Hara K, et al. Evaluation of Ki-67 index in EUS-FNA specimens for the assessment of malignancy risk in pancreatic neuroendocrine tumors. Endoscopy 2014;46(1):32–8.
[19] Zhou B, Zhan C, Xiang J, Ding Y, Yan S. Clinical significance of the preoperative main pancreatic duct dilation and neutrophil-to-lymphocyte ratio in pancreatic neuroendocrine tumors (PNETs) of the head after curative resection. BMC Endocr Disord 2019;19(1):123.
[20] Roche CJ, Hughes ML, Garvey CJ, Campbell F, White DA, Jones L, et al. CT and pathologic assessment of prospective nodal staging in patients with ductal adenocarcinoma of the head of the pancreas. AJR Am J Roentgenol 2003;180(2):475–80.
[21] Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. J Comput Graph Stat 2006;15(3):651–74.
[22] Ellison TA, Wolfgang CL, Shi C, Cameron JL, Murakami P, Mun LJ, et al. A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: a validation of current staging systems and a new prognostic nomogram. Ann Surg 2014;259(2):204–12.
[23] Assi HA, Mukherjee S, Kunz PL, Machiorlatti M, Vesely S, Pareek V, et al. Surgery versus surveillance for well-differentiated, nonfunctional pancreatic neuroendocrine tumors: an 11-year analysis of the national cancer Database. Oncol 2020;25(2):e276–83.
[24] Hashim YM, Trinkaus KM, Linehan DC, Strasberg SS, Fields RC, Cao D, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg 2014;259(2):197–203.
[25] Koh YX, Chok AY, Zheng HL, Tan CS, Goh BK. A systematic review and meta-analysis of the clinicopathologic characteristics of cystic versus solid pancreatic neuroendocrine neoplasms. Surgery 2014;156(1):83–96. e2.
[26] Singhi AD, Chu LC, Tatsas AD, Shi C, Ellison TA, Fishman EK, et al. Cystic pancreatic neuroendocrine tumors: a clinicopathologic study. Am J Surg Pathol 2012;36(11):1666–73.
[27] Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, et al. Prospective study of 68Ga-dotatate positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. J Clin Oncol 2016;34(6):588–96.
[28] Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? Surgery 2016;159(1):320–33.
[29] Morgan RE, Pommier SJ, Pommier RF. Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors. Surgery 2018;163(1):218–25.
[30] Kasai Y, Hirose K, Corvera CU, Kim GE, Hope TA, Shih BE, et al. Residual tumor volume discriminates prognosis after surgery for neuroendocrine liver metastasis. J Surg Oncol 2020;121(2):330–6.
[31] Masui T, Nagai K, Anazawa T, Kasai Y, Sato A, Nakano K, et al. Risk factors for short recurrence-free survival after resection of pancreatic neuroendocrine tumor (PanNET) liver metastases: which patients should undergo resection? Scand J Gastroenterol 2020;55(4):479–84.
[32] Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008;247(3):490–500.
[33] Conrad C, Kutlu OC, Dasari A, Chan JA, Vauthey JN, Adams DB, et al. Prognostic value of lymph node status and extent of lymphadenectomy in pancreatic neuroendocrine tumors confined to and extending beyond the pancreas. J Gastrointest Surg 2016;20(12):1966–74.
[34] Liu P, Zhang X, Shang Y, Lu L, Cao F, Sun M, et al. Lymph node ratio, but not the total number of examined lymph nodes or lymph node metastasis, is a predictor of overall survival for pancreatic neuroendocrine neoplasms after surgical resection. Oncotarget 2017;8(51):89245–55.
[35] Chivukula SV, Tierney JF, Hertl M, Poirier J, Keutgen XM. Operative resection in early stage pancreatic neuroendocrine tumors in the United States: are we over- or undertreating patients? Surgery 2020;167(1):180–6.