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Risk Factors for Recurrence in Pancreatic Neuroendocrine Tumor and Size as a Surrogate in Determining the Treatment Strategy: A Korean Nationwide Study

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Keywords
Pancreas · Neuroendocrine tumor · Risk factor · Recurrence · Treatment algorithm

Abstract
Introduction: The prognostic factors of pancreatic neuroendocrine tumor (PNET) are unclear, and the treatment guidelines are insufficient. This study aimed to suggest a treatment algorithm for PNET based on risk factors for recurrence in a large cohort. ***Methods:*** Data of 918 patients who underwent curative intent surgery for PNET were collected from 14 tertiary centers. Risk factors for recurrence and survival analyses were performed. ***Results:*** The 5-year disease-free survival (DFS) rate was 86.5%. Risk factors for recurrence included margin status (R1, hazard ratio [HR] 2.438; R2, HR 3.721), 2010 WHO grade (G2, HR 3.864; G3, HR 7.352), and N category (N1, HR 2.273). A size of 2 cm was significant in the univariate anal-

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ysis (HR 8.511) but not in the multivariate analysis ($p = 0.407$). Tumor size was not a risk factor for recurrence, but strongly reflected 2010 WHO grade and lymph node (LN) status. Tumors ≤2 cm had lower 2010 WHO grade, less LN metastasis ($p < 0.001$), and significantly longer 5-year DFS (77.9 vs. 98.2%, $p < 0.001$) than tumors >2 cm. The clinicopathologic features of tumors <1 and 1-2 cm were similar. However, the LN metastasis rate was 10.3% in 1-2-cm sized tumors and recurrence occurred in 3.0%. Tumors <1 cm in size did not have any LN metastasis or recurrence. ***Discussion/Conclusion:*** Radical surgery is needed in suspected LN metastasis or G3 PNET or tumors >2 cm. Surveillance for <1-cm PNETs should be sufficient. Tumors sized 1-2 cm require limited surgery with LN resection, but should be converted to radical surgery in cases of doubtful margins or LN metastasis.

Introduction

Unlike pancreatic ductal adenocarcinoma, pancreatic neuroendocrine tumor (PNET) rarely receives the spotlight due to its low incidence [1, 2]. However, this should not be overlooked. First, PNET has a wide spectrum of behavior ranging from indolent to highly malignant. Second, the incidence of PNET has been increasing [2, 3], possibly due to an increased access to cross-sectional imaging and health checkups. Currently, surgical resection is the standard curative treatment for resectable PNETs. However, there are many unanswered questions such as which PNETs require operation, how radical the operation should be, and to what extent should lymph nodes (LN) be harvested.

There are several guidelines on PNET including those from the European Neuroendocrine Tumor Society (ENETS) and the National Comprehensive Cancer Network (NCCN) [4–6]. However, these guidelines tend to be oversimplified. A tumor size of 2 cm is the only criterion that dictates whether a resectable PNET should undergo resection or surveillance. The ENETS suggested that the surgical risk and benefit of resecting small (<2 cm) tumors should be weighed carefully in 2006 [7], and the 2-cm size criterion has been cited often in many studies and guidelines since then. However, the prognostic value of size has not been consistent and fully validated. Furthermore, no other clinical features such as suspicious LN metastasis, which was included as a prognostic factor by ENETS in 2016 [4], are taken into consideration in these guidelines. Moreover, the extent of surgery is very broadly recommended and the need and extent of LN dissection in the current guidelines rely on the surgeon's discretion.

These limitations of the guidelines may be attributed to a poor understanding of the prognostic factors of PNET. With this background, this study aimed to identify risk factors for recurrence based on a large cohort and to suggest a treatment algorithm.

Materials and Methods

Study Design and Data Collection

After obtaining approval from the Institutional Review Board of Seoul National University Hospital (H-1805-123-948), a retrospective study on the PNET cohort was conducted. A written informed consent was waived due to the study's retrospective nature as it poses less than minimal risk to the subjects. Data from 14 tertiary institutions across Korea were collected through the Korean Pancreas Surgery Club (KPSC). Patients who underwent curative intent surgery and were pathologically confirmed with PNET between 2000 and 2017 were identified. The medical records of these patients were reviewed for data collection. The institutions and number of enrolled patients are shown in online suppl. Table 1; see www.karger.com/doi/10.1159/000511875 for all online suppl. material. General demographics and operative data were collected including age, sex, date of operation, type of operation, and presence of distant metastasis at the time of surgery.

Pathologic Data Collection

Pathologic data included multiplicity of tumor, tumor size, Ki-67, mitotic index, 2010 World Health Organization (WHO) grade [8], number of harvested LNs and metastatic LNs, margin status, and TNM stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system [9]. Pathology reports by pathologists with expertise in the study of the pancreas at their respective institution were reviewed for pathologic data collection.

Survival Data

Overall survival was defined as the time interval from the date of surgery to the date of death or the last known follow-up. Disease-free survival (DFS) was defined as the time interval from the date of surgery to the date of first recognition of recurrence or last known follow-up. When analyzing the risk factors, DFS was used since disease-specific mortality could not be obtained. Moreover, since PNET has a relatively good survival, it was uncertain whether the death was caused by PNET.

Statistical Analysis

Continuous variables were presented as the mean ± SD, and categorical variables were presented as frequencies. Fisher's exact test and the χ^2 test were used to compare categorical variables. Survival curves were calculated using the Kaplan-Meier method, and survival differences between groups were evaluated by the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression analysis to examine the risk factors for recurrence of PNET. Results were considered statistically significant if the p value was ≤0.050. Statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM, Armonk, NY, USA).

Results

Overall Characteristics and Survival

Between 2000 and 2017, 918 patients with PNET were identified from 14 institutions. The mean age of the patients was 54.0 ± 12.3 years. There were 432 men and 486 women. PNETs were most frequently found in the body/tail region (58.9%) and were single tumors (96.2%). Pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy were performed in 285 (31.1%), 453 (49.3%), and 23 (2.5%) cases, respectively. Limited pancreatectomy, including enucleation and median pancreatectomy, was performed in 150 patients (16.3%). R0, R1, and R2 resections were achieved in 857 (93.4%), 45 (4.9%), and 16 (1.7%) patients, respectively.

The mean tumor size was 2.8 ± 2.2 cm. According to the 2010 WHO grade, there were 607 G1 (66.1%), 255 G2 (27.8%), and 56 G3 (6.1%) PNETs. LN was not evaluated in 364 patients (39.7%), 439 patients (47.8%) had N0, and 115 patients (12.5%) had N1 stage. Hence, among 553 patients (60.2%) who underwent LN evaluation, the LN metastasis rate was 20.8%. Distant metastasis was found in 34 patients (3.7%) during surgery (Table 1).

The 5- and 10-year survival rates (YSR) were 91.4 and 79.8%, respectively. The 5- and 10-year DFS rates were 86.5 and 79.5%, respectively.

Risk Factors for Recurrence

In the univariate analysis, sex, margin status, size of 2 cm, 2010 WHO grade, T category, N category, and M category were found to be significantly associated with recurrence. Multivariate analysis using these factors revealed that R1 and R2 status (vs. R0; R1: hazard ratio [HR] 2.438, confidence interval [CI]: 1.148–5.178, $p = 0.020$; R2: HR 3.721, CI: 1.472–9.406, $p = 0.005$), 2010 WHO grade (vs. G1; G2: HR 3.864, CI: 2.231–6.694, $p < 0.001$; G3: HR 7.352, CI: 3.784–14.284, $p < 0.001$), and N category (vs. N0; N1: HR 2.273, CI: 1.402–3.687, $p = 0.001$; Nx: HR 0.468, CI: 0.326–0.903, $p = 0.023$) were independent risk factors for recurrence. Of note, despite its significance in univariate analysis, size >2 cm was not significant in the multivariate analysis (HR 2.333, CI: 0.316–17.250, $p = 0.407$) (Table 2).

Role of 2-cm Tumor Size as an Indicator

Among the patients, 453 and 465 patients had tumor sizes ≤2 and >2 cm, respectively. Comparison of the clinicopathologic features showed differences in age, LN retrieval, LN metastasis rate, 2010 WHO grade, T category, N category, M category, recurrence, and death (Table 3).

Table 1. Demographics and clinicopathologic features of 918 pancreatic neuroendocrine tumors

Variable	*N* (%)
Age, years[a]	54.0±12.3
Sex	
Male	432 (47.1)
Female	486 (52.9)
ASA classification	
I	276 (30.1)
II	579 (63.1)
III	62 (6.8)
IV	1 (0.1)
Location	
Head	360 (39.2)
Body/tail	541 (58.9)
Diffuse	17 (1.7)
Multiplicity	
Single	883 (96.2)
Multiple	35 (3.8)
Operation	
Pylorus preserving pancreatoduodenectomy	245 (26.7)
Whipple's operation	40 (4.4)
Distal pancreatectomy	251 (27.3)
Spleen preserving distal pancreatectomy	202 (22.0)
Enucleation	116 (12.6)
Median pancreatectomy	34 (3.7)
Total pancreatectomy	23 (2.5)
Others or unspecified	7 (0.8)
R status	
R0	857 (93.4)
R1	45 (4.9)
R2	16 (1.7)
Size, cm[a]	2.8±2.2
Harvested LN,[a] *n*	9.0±8.6
Metastatic LN,[a] *n*	2.9±3.0
2010 WHO grade	
G1	607 (66.1)
G2	255 (27.8)
G3	56 (6.1)
T category	
T1	416 (45.3)
T2	336 (36.6)
T3	141 (15.4)
T4	25 (2.7)
N category	
Nx	364 (39.7)
N0	439 (47.8)
N1	115 (12.5)
M category	
M0	884 (96.3%)
M1	34 (3.7%)

ASA, American Society of Anesthesiologists; WHO, World Health Organization. [a] Mean ± SD.

Table 2. Univariate and multivariate analysis to identify risk factors for recurrence

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age						
≤40						
>40	0.922	0.523, 1.626	0.779			
Sex						
Male						
Female	0.581	0.387, 0.872	0.009	0.880	0.575, 1.347	0.556
Tumor location						
Head						
Body/tail	0.938	0.627, 1.405	0.757			
Diffuse	0.619	0.085, 4.501	0.636			
Multiplicity						
Single						
Multiple	1.644	0.668, 4.045	0.279			
Margin						
R0						
R1	2.185	1.057, 4.516	0.035	2.438	1.148, 5.178	0.020
R2	3.809	1.543, 9.400	0.004	3.721	1.472, 9.406	0.005
Size						
≤2 cm						
>2 cm	8.511	4.423, 16.378	<0.001	2.333	0.316–17.250	0.407
2010 WHO grade						
G1						
G2	7.299	4.359, 12.220	<0.001	3.864	2.231, 6.694	<0.001
G3	23.649	13.246, 42.225	<0.001	7.352	3.784, 14.284	<0.001
T category						
T1						
T2	5.351	2.592, 11.045	<0.001	1.188	0.149, 9.476	0.871
T3	11.779	5.672, 24.463	<0.001	1.763	0.209, 14.888	0.603
T4	24.596	10.510, 57.561	<0.001	2.889	0.326, 25.625	0.341
N category						
N0						
N1	4.903	3.188, 7.539	<0.001	2.273	1.402, 3.687	0.001
Nx	0.335	0.177, 0.635	<0.001	0.468	0.243, 0.903	0.023
M category						
M0						
M1	5.882	3.389, 10.209	<0.001	1.315	0.728, 2.376	0.364

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization.

Among these, the 2010 WHO grade and N category were independent risk factors for recurrence. The size ≤2-cm group had a significantly higher proportion of G1 and lower proportion of G2/G3 than the size >2-cm group. Moreover, the LN metastasis rate was 27.6 and 8.9% in tumors with sizes >2 and ≤2 cm, respectively (Table 3).

Distant metastasis was found in 3 (0.7%) patients with tumors size ≤2 and 31 (6.7%) with tumor size >2 cm. In terms of outcome, 2.4% experienced recurrence in the size ≤2-cm group compared to 18.7% in the size >2-cm group.

The size ≤2-cm group had better overall survival and DFS than the size >2-cm group. The 5- and 10-YSRs were 95.7 and 90.5% for the size ≤2-cm group and 87.6 and 72.3% for the size >2-cm group, respectively ($p = 0.001$) (Fig. 1a). Likewise, the 5- and 10-year DSF rates were 98.0 and 91.6% for the size ≤2-cm group and 76.4 and 69.1% for the size >2-cm group, respectively ($p < 0.001$) (Fig. 1b)

Subcentimeter PNETs

Tumors ≤2 cm in size were subanalyzed. Tumors <1 cm ($n = 84$) and tumors between 1 and 2 cm ($n = 369$)

Table 3. Comparison of clinicopathologic features according to the size of 2 cm

Variable	≤2 cm (n = 453)	>2 cm (n = 465)	p value
Age			
>40 years	410 (90.5)	389 (83.7)	0.002
≤40 years	43 (9.5)	76 (16.3)	
Sex			
Male	201 (44.4)	231 (49.7)	0.107
Female	252 (55.6)	234 (50.3)	
Tumor location			
Head	162 (35.8)	198 (42.6)	0.070
Body/tail	284 (62.7)	257 (55.3)	
Diffuse	7 (1.5)	10 (2.1)	
Margin			
R0	425 (93.8)	432 (92.9)	0.839
R1	21 (4.5)	24 (5.2)	
R2	7 (1.5)	9 (1.9)	
LN dissection			
Yes	203 (44.8)	351 (75.5)	<0.001
No	250 (55.2)	114 (24.5)	
LN metastasis (n = 554)[a]			
Yes	18 (8.9)	97 (27.6)	<0.001
No	185 (91.1)	254 (72.4)	
2010 WHO grade			
G1	376 (83.0)	231 (49.7)	<0.001
G2	70 (15.5)	185 (39.8)	
G3	7 (1.5)	49 (10.5)	
T category			
T1	416 (91.8)	0 (0.0)	<0.001
T2	37 (8.2)	299 (64.3)	
T3	0 (0.0)	141 (30.3)	
T4	0 (0.0)	25 (5.4)	
N category			
N0	185 (40.8)	254 (54.6)	<0.001
N1	18 (4.0)	97 (20.9)	
Nx	250 (55.2)	114 (24.5)	
M category			
M0	450 (99.3)	434 (93.3)	<0.001
M1	3 (0.7)	31 (6.7)	
Recurrence			
Yes	11 (2.4)	87 (18.7)	<0.001
No	442 (97.6)	378 (81.3)	
Death			
Yes	17 (3.8)	51 (11.0)	<0.001
No	436 (96.2)	414 (89.0)	

Data are represented as n (%). WHO, World Health Organization; LN, lymph node. [a] Nx are excluded.

Table 4. Comparison of clinicopathologic features of <1 cm tumors and tumors between 1 and 2 cm

Variable	<1 cm (n = 84)	1≤ ≤2 cm (n = 369)	p value
Age			
>40 years	83 (98.8)	327 (88.6)	0.004
≤40 years	1 (1.2)	42 (11.4)	
Sex			
Male	40 (47.6)	161 (43.6)	0.507
Female	44 (52.4)	208 (56.4)	
Tumor location			
Head	29 (34.5)	133 (36.0)	0.919
Body/tail	54 (64.3)	230 (62.3)	
Diffuse	1 (1.2)	6 (1.6)	
Margin			
R0	76 (90.5)	349 (94.5)	0.370
R1	6 (7.1)	15 (4.1)	
R2	2 (2.4)	5 (1.4)	
LN dissection			
Yes	29 (34.5)	174 (47.2)	0.036
No	55 (65.5)	195 (52.8)	
LN metastasis (n = 203)[a]			
Yes	0 (0.0)	18 (10.3)	0.082
No	29 (100.0)	156 (89.7)	
2010 WHO grade			
G1	77 (91.7)	299 (81.0)	0.060
G2	6 (7.1)	64 (17.4)	
G3	1 (1.2)	6 (1.6)	
T category			
T1	84 (100.0)	332 (90.0)	0.002
T2	0 (0.0)	37 (10.0)	
T3	0 (0.0)	0 (0.0)	
T4	0 (0.0)	0 (0.0)	
N category			
N0	29 (34.5)	156 (42.3)	0.029
N1	0 (0.0)	18 (4.9)	
Nx	55 (65.5)	195 (52.8)	
M category			
M0	84 (100.0)	366 (99.2)	1.000
M1	0 (0.0)	3 (0.8)	
Recurrence			
Yes	0 (0.0)	11 (3.0)	0.230
No	84 (100.0)	358 (97.0)	
Death			
Yes	2 (2.4)	15 (4.1)	0.138
No	82 (97.6)	354 (95.9)	

Data are represented as n (%). WHO, World Health Organization; LN, lymph node. [a] Nx are excluded.

were compared. Although statistically significances were not reached, there were marginal differences in the 2010 WHO grade distributions (p = 0.060) and LN metastasis rates (p = 0.082). Of the 84 cases with tumors <1 cm, 91.7% were G1 and only 1 case was G3. There was no LN metastasis, distant metastasis, or recurrence in these tumors. In contrast, tumors between 1 and 2 cm had a LN metastasis rate of 10.3% and accounted for all 11 cases of recurrences in tumors ≤2 cm (Table 4).

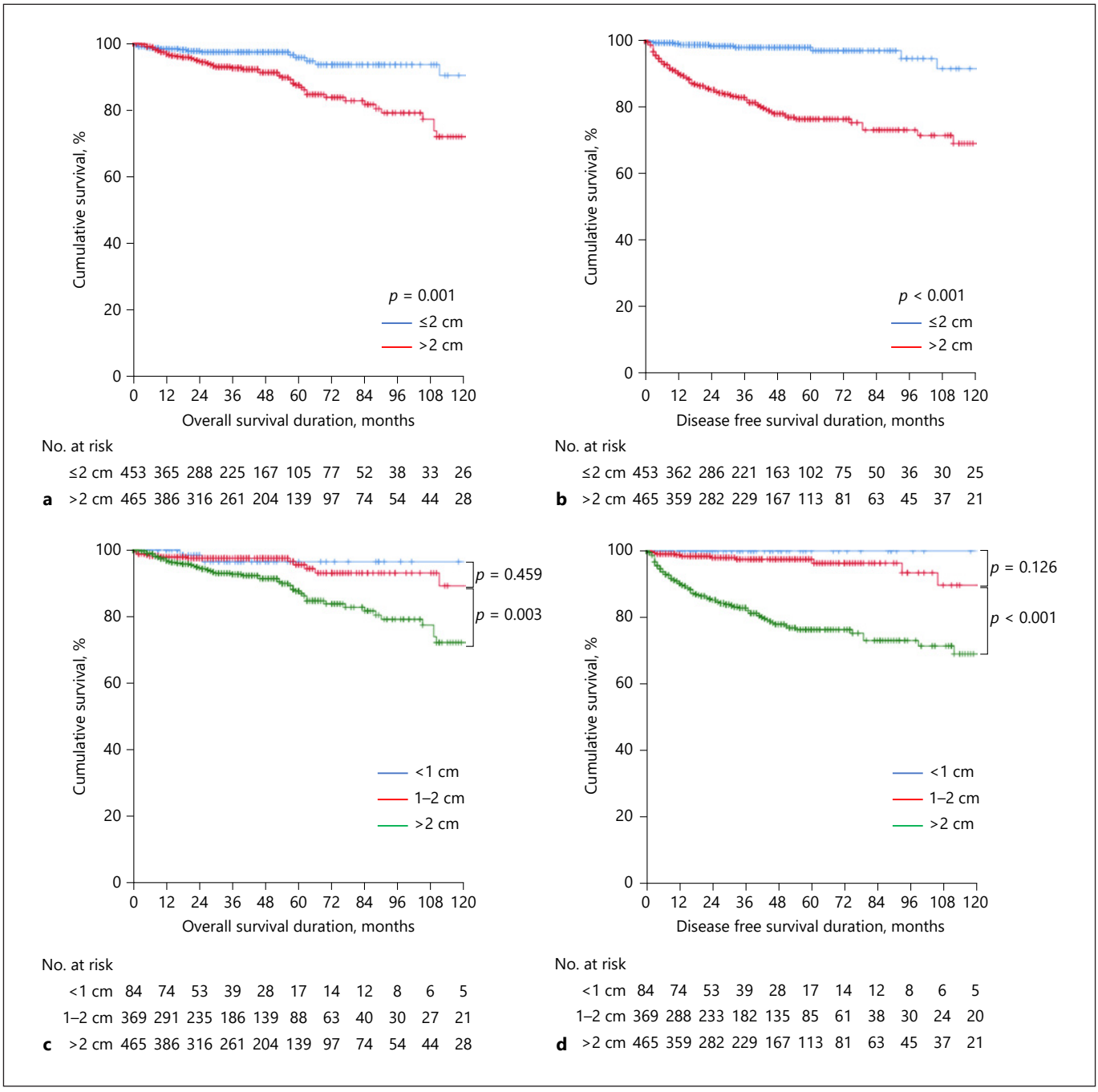

Fig. 1. Comparison of survival between tumors of different sizes. Overall survivals of tumors ≤2 cm and tumors >2 cm (**a**), disease-free survivals of tumors ≤2 cm and tumors >2 cm (**b**), overall survivals of tumors <1 cm, tumors between 1 and 2 cm, and tumors >2 cm (**c**), and disease-free survivals of tumors <1 cm, tumors between 1 and 2 cm, and tumors >2 cm (**d**).

The overall survival curves were not significantly different ($p = 0.459$). The 5- and 10-YSRs were both 96.5% for tumors <1 cm. For tumors between 1 and 2 cm, the 5- and 10-YSRs were 95.6 and 89.2%, respectively (Fig. 1c).

The DFS curves were not significantly different ($p = 0.126$). The 5- and 10-year DFS rates were all 100% for tumors <1 cm and 97.5 and 89.7% for tumors between 1 and 2 cm, respectively (Fig. 1d).

LN as an Indicator

Among 554 patients whose LN was evaluated, patients with N0 ($n = 439$) and N1 ($n = 115$) were compared. These patients differed significantly in terms of tumor size, 2010 WHO grade, T category, N category, M category, recurrence, and death. Patients with N1 had worse features including larger tumors, higher 2010 WHO grades, higher T category, more distant metastasis at surgery, higher recurrence rate, and more deaths than patients with N0 (Table 5).

N0 patients had significantly better overall survival ($p < 0.001$) and DFS ($p < 0.001$) than N1 patients. The 5- and 10-YSRs of N0 were 92.2 and 79.3%, respectively, and those of N1 were 71.2 and 51.9%, respectively (Fig. 2a). The 5- and 10-year DFS rates of N0 were 87.5 and 82.5%, respectively, whereas those of N1 were 47.7 and 19.9%, respectively (Fig. 2b).

Table 5. Comparison of clinicopathologic features of 554 patients with LN evaluation

Variable	N0 ($n = 439$)	N1 ($n = 115$)	p value
Age			
>40 years	378 (86.1)	100 (87.0)	0.813
≤40 years	61 (13.9)	15 (13.0)	
Sex			
Male	199 (45.3)	61 (53.0)	0.140
Female	240 (54.7)	54 (47.0)	
Tumor location			
Head	233 (53.1)	57 (49.6)	0.342
Body/tail	197 (44.9)	53 (46.1)	
Diffuse	9 (2.0)	5 (4.3)	
Margin			
R0	420 (95.7)	108 (93.9)	0.458
R1	13 (2.9)	6 (5.2)	
R2	6 (1.4)	1 (0.9)	
Size (2 cm)			
≤2 cm	185 (42.1)	18 (15.7)	<0.001
>2 cm	254 (57.9)	97 (84.3)	
Size (1 cm)			
<1 cm	29 (6.6)	0 (0.0)	0.005
≥1 cm	410 (93.4)	115 (100.0)	
2010 WHO grade			
G1	275 (62.6)	37 (32.2)	<0.001
G2	146 (33.3)	48 (41.7)	
G3	18 (4.1)	30 (26.1)	
T category			
T1	171 (39.0)	16 (13.9)	<0.001
T2	178 (40.5)	55 (47.8)	
T3	76 (17.3)	38 (33.1)	
T4	14 (3.2)	6 (5.2)	
M category			
M0	429 (97.7)	95 (82.6)	<0.001
M1	10 (2.3)	20 (17.4)	
Recurrence			
Yes	45 (10.3)	41 (35.7)	<0.001
No	394 (89.7)	74 (64.3)	
Death			
Yes	34 (7.7)	23 (20.0)	0.001
No	405 (92.3)	92 (80.0)	

Data are represented as *n* (%). WHO, World Health Organization; LN, lymph node.

Discussion/Conclusion

This study is one of the largest cohort studies on PNET excluding those using statistical databases such as Surveillance, Epidemiology, and End Results which have a higher probability of coding errors and lack some important data. This study found that the risk factors for recurrence were positive margins status, higher 2010 WHO grade, and LN metastasis. Size was not an independent risk factor for recurrence but reflected these risk factors: 2010 WHO grade and LN metastasis. Therefore, this study supports the use of size as an indicator in establishing a treatment strategy for resectable PNET. Based on this, this study proposes the following treatment algorithm: radical surgery should be suggested in cases with a risk of LN metastasis on cross-sectional imaging and/or G3 tumor documented through endoscopic biopsy. In addition, tumors >2 cm should be indicated for radical surgery. Since tumors between 1 and 2 cm have a measurable LN metastasis rate, surgery with LN resection should be favorable over surveillance. However, given the small size, limited pancreatectomy may be sufficient where possible. For PNETs <1 cm, surveillance can be safely applied. This treatment algorithm is shown in Figure 3.

The ENETS consensus guidelines of 2012 found distant metastasis, WHO grade, age ≥40 years, margin status, rapid progression of liver metastasis, and bone metastasis as the prognostic factors of PNET [10]. LN metastasis and LN ratio were only recently added to the 2016 ENETS guidelines, based on several studies [4, 11–14]. Various prognostic factors have been reported in many studies, as reviewed by Bilimoria et al. [15]. Based on these studies and the ENETS consensus guidelines, the most consistent prognostic factors seem to be the 2010 WHO grade, LN metastasis, margin status, and distant metastasis. The present nationwide study using 918 patients found that margin status, 2010 WHO grade, and N category were independent risk factors for recurrence in resected PNET, which is consistent with the ENETS consensus guidelines and several previous studies [4, 10, 15].

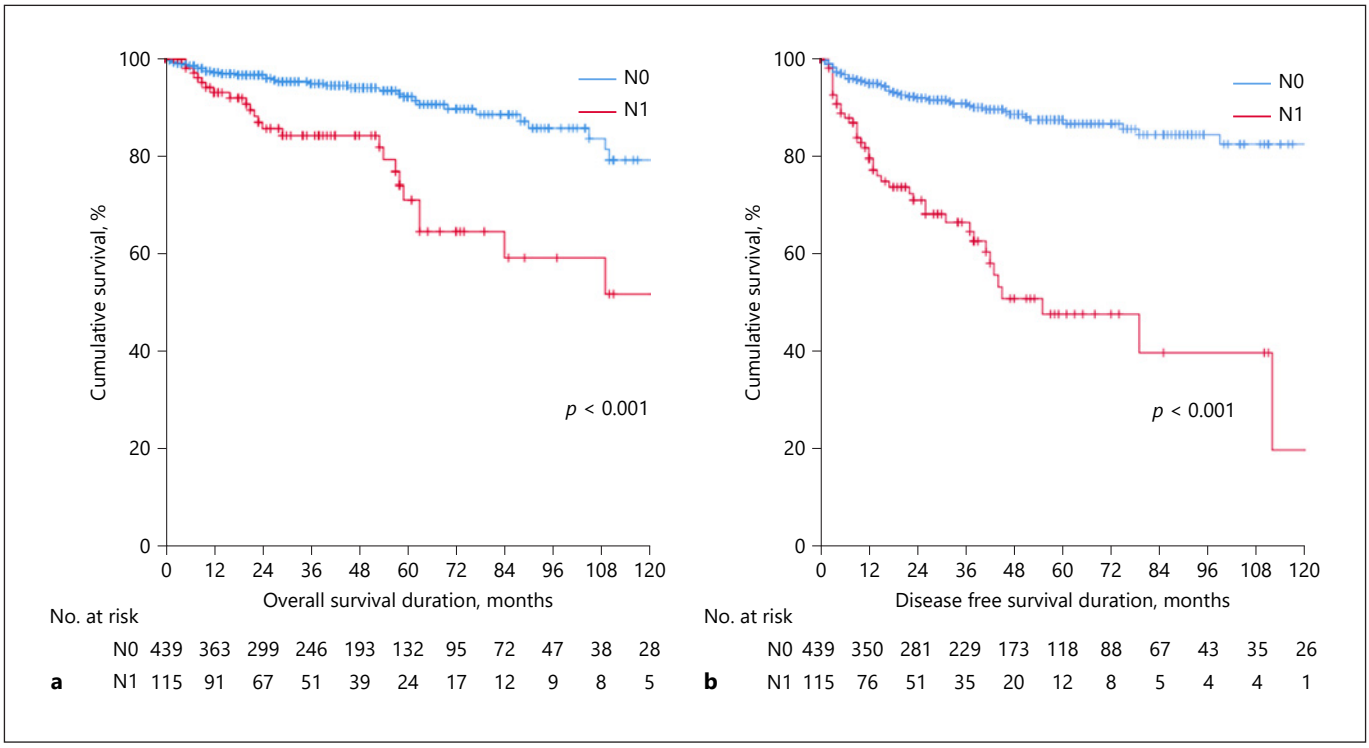

Fig. 2. Comparison of survival curves of N0 and N1 PNETs. Overall survival (**a**) and disease-free survival (**b**). PNET, pancreatic neuroendocrine tumor.

Among these, 2010 WHO grade was the most powerful indicator and had the largest HR and has been the most consistent factor [15–18].

In the most widely used guidelines, none of the prognostic factors are used in deciding treatment. Instead, size seems to be the major determinant. The most recent ENETS consensus guidelines recommend surgery for tumors >2 cm and offers 2 options for tumors that are 2 cm or less: surveillance or surgery depending on 2010 WHO grade, symptoms, and patients' wishes [4]. The NCCN guidelines recommend radical surgery for tumors >2 cm or those with positive LNs. The guidelines for tumors ≤2 cm are not clear and include observation, enucleation, distal pancreatectomy, or pancreatoduodenectomy [5]. Why is tumor size used as an indicator of surgery despite being an inconsistent prognostic factor?

In the present study, although size was significantly associated with recurrence in the univariate analysis, it was not an independent risk factor for recurrence in the multivariate analysis. In a review by Bilimoria et al. [15], only 3 out of 16 studies reported that size adversely affected survival in the univariate analysis [19–21]. Even in these 3 studies, cutoff values were all different ranging from 2 to 4 cm. In addition, among 9 multivariate analyses, only 1 study by Hochwald et al. [22] reported size as an independent prognostic factor. However, the sample size of these studies was 184 or less. Furthermore, Bilimoria et al. [15] studied 3,851 patients from the National Cancer Database and did not find size as an independent prognostic factor. Therefore, the use of size as an indicator for treatment strategy is questionable.

Despite not qualifying as an independent risk factor for recurrence, when comparing tumors >2 cm and those ≤2 cm, an evident and significant difference in the distribution of 2010 WHO grade and LN metastasis was observed. In tumors ≤2 cm, only 1.5% were G3 while 83.0% were G1; however, in tumors >2 cm, 10.5% were G3 tumors. Moreover, the LN metastasis rate was 8.9% in tumors ≤2 cm, whereas it was 27.6% in tumors >2 cm. Thus, although size was not an independent risk factor for recurrence, it reflected other important factors including 2010 WHO grade and LN metastasis. The 2010 WHO grade and LN metastasis can be determined postoperatively in the majority of cases. In the absence of this information preoperatively, size may be used as a surrogate of WHO 2010 grade and LN metastasis in establishing the treatment

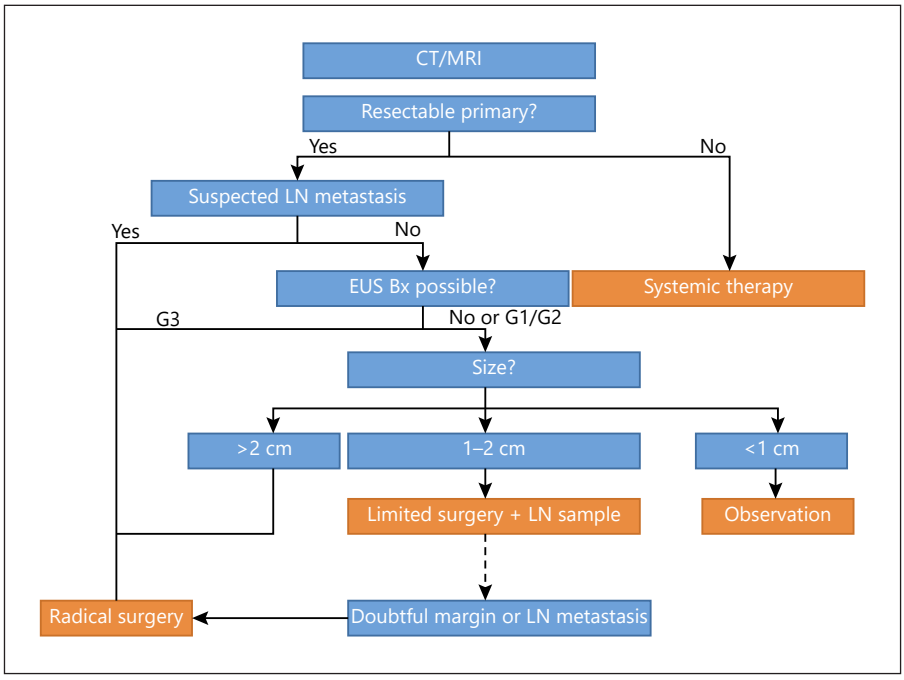

Fig. 3. Proposed treatment algorithm based on the identified prognostic factors and clinicopathologic features of tumors according to different size criteria. LN, lymph node.

strategy. However, if the WHO grade can be determined through endoscopic biopsy or lymphadenopathy is highly suspected in the imaging or is biopsy proven, these findings should have priority over size in the decision-making.

While tumors ≤2 cm have more benign characteristics as shown in this study and other previous reports [23–26], there persist concerns against surveillance based on reports of malignancy even in small PNETs [27–29]. The present study found that 17.0% of tumors ≤2 cm were G2 and G3 tumors and the LN metastasis rate was 8.9% in these tumors, which are not negligible. Further subgroup analysis of tumors <1 cm found that these tumors had only 1 case of G3 tumor and no LN metastasis, distant metastasis, or recurrence. In contrast, tumors between 1 and 2 cm had an LN metastasis rate of 10.3 and 19.0% of them were G2/3 tumors. Therefore, it may be safer to recommend a surveillance policy for tumors <1 cm and perform limited pancreatectomy for tumors between 1 and 2 cm. Of note, while median pancreatectomy had a comparable R1/2 rate (0%), enucleation had a significantly higher R1/2 rate compared to other types of surgery (21.6 vs. 4.5%, $p < 0.001$, result not shown). This could be due to difficulty in determining the margin status for tumors enucleated along the tumor capsule rather than true R1/2 as the recurrence rate of enucleation was significantly lower than others (0.9 vs. 12.1%, $p < 0.001$, result not shown). Nevertheless, patients should be carefully selected when considering enucleation. Radical surgery such as pancreatoduodenectomy or distal pancreatectomy should be recommended for tumors >2 cm because of the substantial risk of malignancy.

Not much is known about the extent of LN retrieval. In the ENETS consensus guidelines for surgery for PNET, routine LN resection is recommended for tumors >2 cm [30]. In the NCCN guidelines, tumors >2 cm are recommended for regional LN resection [5]. However, LN resection for tumors <2 cm is unclear in both guidelines. The ENETS guidelines do not clearly address the issue of PNET <2 cm [4, 30]. The NCCN guidelines state that LN resection should be "considered" for risk of LN metastases and is indicated as "±regional nodes" in their algorithm [5]. This study found that LN metastasis was an important risk factor for recurrence. Thus, the importance of LN evaluation during surgery should be emphasized for predicting patient's prognosis. In addition, LN resection should be performed for curative purposes, especially in tumors >2 cm where LN metastasis was present in 27.6%. LN resection should be performed not only for large tumors but also for tumors ≤2 cm, particularly in tumors between 1 and 2 cm, which had a metastasis rate of 10.3%. A recent multicenter study from the US Neuroendocrine Tumor Study Group and a large-scale meta-analysis also demonstrated 9 and 11.5% LN metastasis rates in small PNETs, respectively, hence, recommending LN resection for small PNETs [31, 32]. LN resection may be omitted for tumors <1 cm in the absence of suspicious LN, in which LN metastasis was rare.

The implication of LN resection in terms of benefit and risk is difficult to determine. Those who underwent LN resection did not benefit in terms of DFS (5-year: 79.6 vs. 96.5%, $p < 0.001$) and reducing recurrence rate (15.5 vs. 3.3%, $p < 0.001$) while experiencing more complications (35.4 vs. 25.3%, $p < 0.001$) compared to those who did not. However, these are likely to be confounded by more severe disease and thus more extensive operation. The role of LN resection in preventing local recurrence is also questionable as 86.3% of the recurrences occurred as distant metastases such as the liver and distant LNs and seldom in the regional LNs. In 11 recurrences in patients who did not undergo LN resection, there was no recurrence in regional LNs, whereas 9 occurred at distant sites and 2 in the remnant pancreas. Even so, regional LN resection should be performed for prognosis prediction and curative purposes.

This study has several limitations. First, the present study was a retrospective analysis. Given the low incidence of PNET, the use of a retrospective cohort to reassess the risk factors and investigate the clinicopathologic features is unavoidable. Second, the study population was limited to resected PNET. Therefore, the results are not representative of unresectable, systemic, and observed small PNETs. Third, the 2010 WHO grade was used although the 2017 WHO grade [33] has been published. However, as the new grade divides G3 PNET into well-differentiated G3 PNET and neuroendocrine carcinoma, applying the 2010 WHO grade does not seem to hinder our understanding of PNETs. Fourth, staging may be understaged, especially in terms of metastasis. Somatostatin receptor scintigraphy, which is becoming more popular, was not used in many cases. Fifth, the effect of adjuvant treatment was not discussed. However, an adjuvant strategy for PNET has not yet been established and standardized [34] and thus remains an area to be explored in the future. Finally, tumors between 1 and 2 cm still remain as a vast gray zone. While limited resection was recommended due to about 20% prevalence of G2/3 tumor and 10% LN metastasis, about 80% of the patients may be at risk of unnecessary operation. Future studies should focus on enhancing our ability to predict high-risk tumors between 1 and 2 cm.

This study has important implications for understanding PNET. The results of this study provide more robust evidence on risk factors for recurrence in PNET. In addition, this study justified the use of size in guiding treatment and provided a firm basis for continued utilization. Finally, this study proposes a treatment algorithm taking into consideration the clinicopathologic features according to all of the risk factors for recurrence and size. This algorithm will complement the current guidelines which tend to be oversimplified.

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Statement of Ethics

This study was approved by the Institutional Board of Review of Seoul National University Hospital (H-1805-123-948) and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Waiver of written informed consent was approved by the Institutional Board of Review of Seoul National University Hospital as the study was determined to pose less than minimal risk to the subjects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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