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ORIGINAL ARTICLE

Significance of lymph node metastasis in pancreatic neuroendocrine tumor

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Abstract

Purpose Pancreatic neuroendocrine tumor (PNET) is relatively rare and has a generally better prognosis than does pancreatic cancer. However, as its prognosis in patients with lymph node metastasis (LNM) is unclear, lymph node dissection for PNET is controversial. Our study aimed to clarify the significance of LNM in PNET.

Methods We retrospectively examined 83 PNET patients who underwent pancreatic resections with lymph node dissection at Kumamoto University Hospital, Saiseikai Kumamoto Hospital, and Kumamoto Regional Medical Center from April 2001 to December 2014. Their clinicopathological parameters were analyzed by the absence or presence of LNM, and with regard to the disease-free survival (DFS) and overall survival (OS). A predictive score of LNM was also made using the age, tumor size, primary tumor location, and tumor function.

Results Although the 5-year OS was 74.8% for LNM$^+$ and 94.6% for LNM$^-$ ($P=0.002$), LNM was not an independent risk factor for the OS in a multivariate analysis. However, tumors larger than 1.8 cm were found to be an independent prognostic factor, and the cut-off value for the predictive score was 1.69.

Conclusions Although LNM was not an independent prognostic factor, lymph node dissection is recommended for patients whose predictive score is larger than 1.69.

Keywords Pancreas · Neuroendocrine tumor · Pancreatic neuroendocrine tumor · Lymph node metastasis · Prognosis

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Introduction

Pancreatic neuroendocrine tumor (PNET) is uncommon, and its prognosis is generally better than that of pancreatic cancer [1, 2]. Although some PNET patients have lymph node metastasis (LNM), its effect on their prognosis is unclear. The prognosis for PNET has been associated with the tumor location and histological differentiation [1].

Parek et al. evaluated the predictive value of lymph node sampling and LNM for PNET [3] and found that race, functional status and metastatic disease were associated with LNM in a univariate analysis, but only distant disease (and not tumor size) predicted LNM in a multivariate analysis. While some investigations of factors that predict the outcomes in PNET have been conducted, lymph node dissection for PNET remains controversial [4–8].

Therefore, in this study, we aimed to clarify the significance of LNM in PNET.

Methods

Patients and diagnoses

All patients underwent pancreatic resection for PNET at Kumamoto University Hospital, Saiseikai Kumamoto Hospital, or Kumamoto Regional Medical Center from April

2001 to December 2014. From a total of 94 patients, we excluded 11 patients who did not undergo lymph node dissection, leaving 83 patients who underwent lymph node dissection in this analysis. The patients underwent imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), for the diagnosis before operation. The final diagnoses were confirmed pathologically using resected specimens. Only a PNET patient with liver metastasis underwent pancreatic resection and liver resection who was clinically diagnosed to have both pancreatic cancer and hepatocellular carcinoma before the operation. Tumors were classified as functional PNET according to the clinical signs and symptoms of hormonal excess and the increased levels of corresponding serum peptides and hormones. Tumors were classified as non-functional if they were not associated with distinct clinical manifestations or hormone alterations [9].

Treatment

Surgical procedures were selected based on each tumor's location and extent and the patient's general condition. Pancreatic resection was considered the first-choice treatment for patients with PNET.

Estimated risk factors for the survival and recurrence

Follow-up information was collected from clinical records at each hospital. The interval times of follow-up after surgery were every 3 months. The duration of the overall survival (OS) was calculated from the surgery date to the tumor-specific death or the patient's last follow-up. The relapse time [disease-free survival (DFS)] was calculated from the surgery date to the date when recurrence was diagnosed. We analyzed seven variables: age, sex, tumor size, primary tumor location, tumor function, regional LNM, and 2010 World Health Organization (WHO) classification. We set the tumor size cutoff at 1.8 cm, based on the median size.

Estimated risk factors for LNM

We analyzed four variables to predict LNM: the age, tumor size, primary tumor location, and tumor function. We calculated the predictive score of LNM using these variables.

Statistical analyses

Discrete and continuous variables were compared using the χ^2 and Student's t tests, respectively. We analyzed the DFS

and OS by the Kaplan–Meier method; differences were analyzed by the log-rank test. To estimate the risk factors for the survival and recurrence using a Cox proportional hazards regression analysis, continuous variables were converted to binary variables. To estimate the risk factors of LNM using a logistic regression analysis, continuous variables were converted to binary variables as well. All analyses were performed using the JMP software program (Release 10.0.2; SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Ethical standards

The study protocol was approved as number 1120 by the Institutional Review Board of Kumamoto University Hospital.

Results

Clinicopathological characteristics

Among 83 patients, 38 (45.8%) were male, and 45 (54.2%) were female. The median age was 57 years (range: 17–84 years; Table 1). The median tumor size was 1.8 cm (range: 0.5–9.0 cm). At the diagnosis, 66 patients (79.5%) presented with no LNM (N⁻), and 17 patients (20.5%) presented with LNM (N⁺). We found that 67.5% of PNETs were located in the distal pancreas and 32.5% in the head. Of the 21 patients (25.3%) who had functional PNET, the most frequent functional PNET entity was insulinoma (19.3%), followed by glucagonoma (2.4%), gastrinoma (1.2%), VIPoma (1.2%), and PPoma (1.2%). Their 2010 WHO classifications were G1: 53.0%; G2: 27.7%; and G3 (neuroendocrine carcinoma): 8.4%.

A comparison of the clinicopathological characteristics between patients with N⁻ disease and those with N⁺ disease is also summarized in Table 1. Patients with N⁺ PNET had larger tumors than did the N⁻ PNET group ($P = 0.013$). Interestingly, N⁺ PNETs were significantly more likely to be located in the proximal pancreas than were N⁻ PNETs ($P = 0.010$). The WHO classification was strongly correlated with regional LNM, with N⁻ PNET more likely to be of a lower grade than N⁺ PNET; N⁻ PNET accounted for 88.7% (39/44) of G1 cases, 69.6% (16/23) of G2 cases, and 28.6% (2/7) of G3 cases ($P = 0.003$, Pearson's χ^2 test). Patients with non-functional PNET tended to have N⁺ disease, although not to a significant degree ($P = 0.126$).

Surgical procedures

Among the 83 patients, 2 (2.4%) received subtotal pancreatectomies, 50 (60.2%) received distal pancreatectomies, 27

Table 1 Clinicopathological characteristics of 83 patients with node-negative (N⁻) or node-positive (N⁺) pancreatic neuroendocrine tumor

	Total (n = 83)	N⁻ (n = 66)	N⁺ (n = 17)	P value
Median age, years (range)	57 (17–84)	57 (17–79)	58 (18–84)	0.381
Sex, n (%)				
Male	38 (45.8)	27 (40.9)	11 (64.7)	0.079
Female	45 (54.2)	39 (59.1)	6 (35.3)	
Tumor size, median, cm (range)	1.8 (0.5–9.0)	1.5 (0.6–9.0)	3.0 (0.5–6.0)	0.013
Location of primary tumor, n (%)				
Ph	27 (32.5)	17 (25.8)	10 (58.8)	0.010
Pb, Pt	56 (67.5)	49 (74.2)	7 (41.2)	
Non-functional, n (%)	62 (74.7)	47 (71.2)	15 (88.2)	0.126
Functional, n (%)	21 (25.3)	19 (28.8)	2 (11.8)	
Insulinoma	16 (19.3)	15 (22.7)	1 (5.9)	
Gastrinoma	1 (1.2)	0 (0)	1 (5.9)	
Glucagonoma	2 (2.4)	2 (3.0)	0 (0)	
VIPoma	1 (1.2)	1 (1.5)	0 (0)	
PPoma	1 (1.2)	1 (1.5)	0 (0)	
WHO classification 2010, n (%)				
G1	44 (53.0)	39 (59.1)	5 (29.4)	0.003
G2	23 (27.7)	16 (24.2)	7 (41.2)	
G3	7 (8.4)	2 (3.0)	5 (29.4)	
Unknown	9 (10.8)	9 (13.6)	0 (0)	
Surgical procedure, n (%)				
Subtotal pancreatectomy	2 (2.4)	2 (3.0)	0 (0)	0.029
Distal pancreatectomy	50 (60.2)	43 (65.2)	7 (41.2)	
Pancreatoduodenectomy	27 (32.5)	17 (25.8)	10 (58.8)	
Local/partial pancreatectomy	4 (4.8)	4 (6.0)	0 (0)	
No recurrence, n (%)	67 (80.7)	57 (86.4)	10 (58.8)	0.016
Recurrences, n (%)	16 (19.3)	9 (13.6)	7 (41.2)	
Regional lymph node metastasis	1 (1.2)	0 (0)	1 (5.9)	
Liver metastasis	11 (13.3)	7 (10.6)	4 (23.5)	
Lymph node and liver metastases	3 (3.6)	1 (1.5)	2 (11.8)	
Remnant pancreas	1 (1.2)	1 (1.5)	0 (0)	

(32.5%) received pancreatoduodenectomies, and 4 (4.8%) received local or partial pancreatectomies. The patients who received distal pancreatectomies and pancreatoduodenectomies were more likely to have LNM than those who underwent other procedures (P = 0.029; Table 1).

Recurrence

Among the 83 patients, a total of 16 (19.3%) recurrences occurred, and their patterns are summarized in Table 1. Liver metastases were observed most often (13.3%), while regional lymph node metastases alone was the least frequently observed pattern (1.2%). The combination of both lymph node and liver metastases accounted for 3.6% of cases. N⁺ PNETs were significantly more likely to recur than were N⁻ PNETs (P = 0.016). Interestingly, no patients with N⁻ PNETs had lymph node recurrence.

The survival stratified by LNM and tumor size

During the follow-up period, eight patients died of recurrence or progression of primary tumor, and two patients died of other causes. The 5-year DFS rates were not significant for node positivity (N⁺: 60.5% and N⁻: 83.8%; P = 0.052; Fig. 1a), while the 5-year OS rates were significant for positivity (N⁺: 74.8% and N⁻: 94.6%; P = 0.002; Fig. 1b). The 5-year DFS rates were significant for tumor size (>1.8 cm: 63.0% and ≤1.8 cm: 95.2%; P = 0.002; Fig. 1c); the 5-year OS rates were also significant for tumor size (>1.8 cm: 79.5% and ≤1.8 cm: 100%; P = 0.001; Fig. 1d).
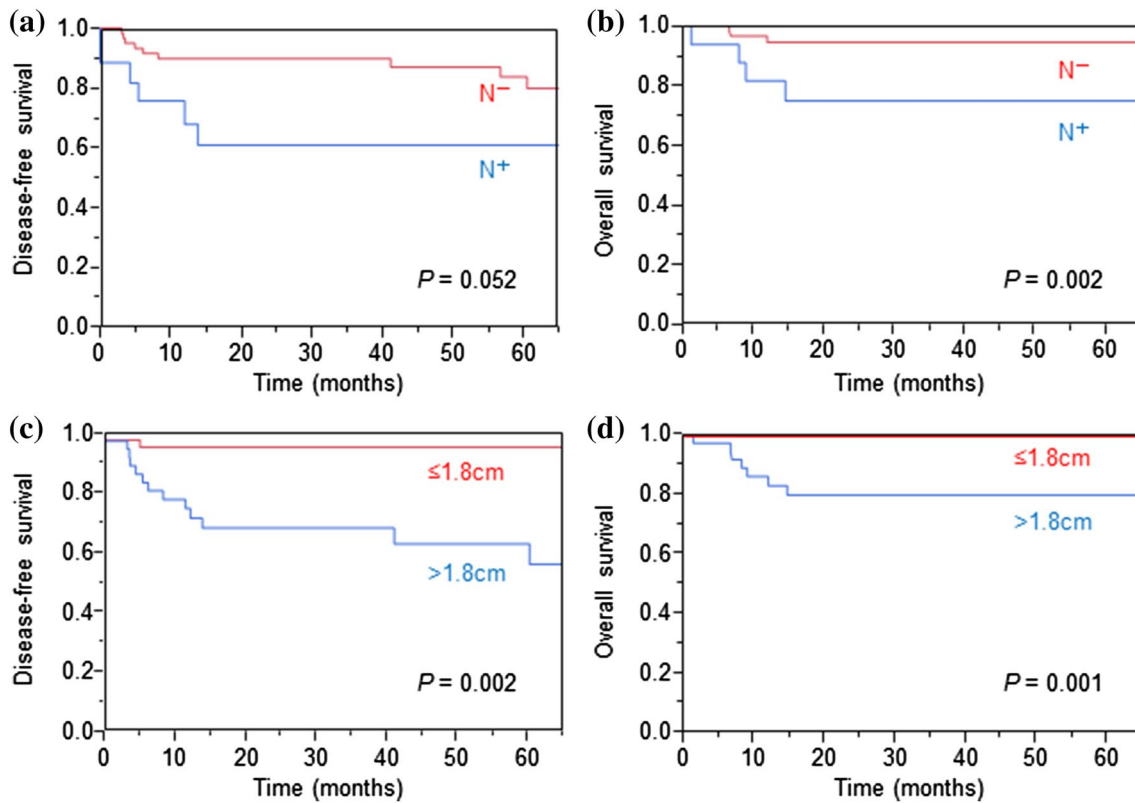
Fig. 1 Kaplan–Meier survival curves by lymph node metastasis (LNM) and tumor size. **a** Comparison of the disease-free survival (DFS) between patients with LNM (N$^+$; $n=17$) and without LNM (N$^-$; $n=66$). The DFS did not significantly differ between N$^+$ patients and N$^-$ patients ($P=0.052$). **b** Comparison of the overall survival (OS) between N$^+$ patients ($n=17$) and N$^-$ patients ($n=66$). The N$^+$ patients had a significantly shorter OS than did the N$^-$ patients

($P=0.002$). **c** Comparison of the DFS between patients with tumor size >1.8 cm ($n=38$) and ≤1.8 cm ($n=45$). Patients with tumor size >1.8 cm had a significantly shorter DFS than did those with tumor size ≤1.8 cm ($P=0.002$). **d** Comparison of the OS between patients with tumor size >1.8 cm ($n=38$) and ≤1.8 cm ($n=45$). Patients with tumor size >1.8 cm had a significantly shorter OS than did those with tumor size ≤1.8 cm ($P=0.001$)

Univariate and multivariate analyses of factors affecting the DFS and OS

Factors associated with the DFS were evaluated by univariate and multivariate analyses. A univariate analysis showed that male sex [hazard ratio (HR): 3.17; $P=0.026$], tumor size >1.8 cm (HR: 6.12; $P=0.001$), and NET G3 (HR: 8.79; $P=0.003$) were significant variables influencing a poor DFS (Table 2). However, only tumor size >1.8 cm (HR: 3.86; $P=0.040$) remained an independent risk factor for the DFS in a subsequent multivariate analysis (Table 2).

Factors associated with the OS were also evaluated by univariate and multivariate analyses. In the univariate analysis, male sex (HR: 11.5; $P=0.003$), tumor size >1.8 cm [HR: not applicable (NA); $P<0.001$], non-functional PNET (HR: NA; $P=0.018$), regional LNM (HR: 6.89; $P=0.005$), and NET G3 (HR: 25.7; $P<0.001$) were significantly associated with a poor OS, but only tumor size >1.8 cm (HR:

NA; $P=0.015$) remained an independent risk factor for the OS in a subsequent multivariate analysis (Table 3).

Risk model of factors affecting LNM

We developed a risk model of factors associated with LNM. The logistic model is presented in Table 4. A univariate analysis showed that tumor size >1.8 cm [odds ratio (OR): 5.33; $P=0.008$] and the primary tumor location (OR: 4.12; $P=0.013$) were significant variables influencing LNM. However, only tumor size >1.8 cm (OR: 4.14; $P=0.030$) remained an independent risk factor for LNM in a subsequent multivariate analysis. We also presented the predictive score of LNM in Table 4.

To evaluate the model performance, the area under the receiver-operating characteristic curve (AUROC) was calculated for the validation sets. The AUROC for LNM was 0.78. Details of the model performance metrics for LNM

Table 2 Univariate and multivariate analyses of factors affecting the disease-free survival in patients with PNET (*n* = 83)

	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)					
>57	41	2.19 (0.79–6.95)	0.133		
≤57	42				
Sex					
Male	38	3.17 (1.15–10.1)	0.026	2.60 (0.77–9.52)	0.123
Female	45				
Tumor size (cm)					
>1.8	38	6.12 (1.96–26.8)	0.001	3.86 (1.06–18.2)	0.040
≤1.8	45				
Location of primary tumor					
Ph	27	1.28 (0.44–3.46)	0.633		
Pb, Pt	56				
Functional PNET					
Yes	21	1.47 (0.46–4.07)	0.491		
No	62				
Regional lymph node metastasis					
Yes	17	2.63 (0.89–7.08)	0.077	1.00 (0.31–3.10)	0.999
No	66				
WHO classification 2010					
G3	7	8.79 (2.29–29.0)	0.003	3.40 (0.81–12.9)	0.090
G1, G2	67				
Unknown	9				

CI confidence interval, *HR* hazard ratio, *PNET* pancreatic neuroendocrine tumor

Table 3 Univariate and multivariate analyses of factors affecting the overall survival in patients with PNET (*n* = 83)

	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)					
>57	41	1.75 (0.46–8.31)	0.416		
≤57	42				
Sex					
Male	38	11.5 (2.09–212.7)	0.003	7.17 (0.89–153.4)	0.065
Female	45				
Tumor size (cm)					
>1.8	38	NA (5.01–5.01)	<0.001	NA (1.81–NA)	0.015
≤1.8	45				
Location of primary tumor					
Ph	27	2.51 (0.66–10.1)	0.170		
Pb, Pt	56				
Functional PNET					
No	62	NA (1.54–1.54)	0.018	NA (0.38–NA)	0.183
Yes	21				
Regional lymph node metastasis					
Yes	17	6.89 (1.8–32.8)	0.005	1.08 (0.23–6.15)	0.926
No	66				
WHO classification 2010					
G3	7	25.7 (5.28–140.0)	<0.001	4.68 (0.94–27.6)	0.059
G1, G2	67				
Unknown	9				

CI confidence interval, *HR* hazard ratio, *NA* not applicable, *PNET* pancreatic neuroendocrine tumor

are displayed in Fig. 2. We set 1.69 as the cut-off value (sensitivity: 0.88 and specificity: 0.61).

Discussion

Diagnosing LNM in PNET patients before surgery is difficult, unless the metastatic tumors are fairly large. We perform contrast CT, MRI, and EUS for PNET patients at our institution. However, LNM in PNET patients is rarer than liver metastasis. Positron emission tomography (PET)-CT can be used to diagnose malignant tumors, but not all PNETs. Therefore, it is very difficult to detect LNM before surgery. However, not all PNET patients have LNM, and the prognosis of PNET is not very poor. The previous studies have focused on the LNM incidence and/or prognosis based on the tumor size [5, 10–15]. Although LNM has been seen even in patients with tumors <1.0 cm, LNM occurs more often with large tumors than with smaller ones. In our study, LNM was most often seen with pancreatic head tumors, although this finding has not been consistent across studies [6, 16]. Several studies of independent prognostic

factors for resected PNET have found that the presence of tumor necrosis and lymphatic or hepatic metastases affects the DFS [17]. Some reports have associated LNM with a shorter DFS or OS [16, 18–21], while other studies have found that the lymph node status did not affect the survival [3, 4, 22, 23]. The age, grade of tumor, and presence of distant metastases predict worse outcomes [24]. As such, the resection status may not affect the survival [25].

Our findings suggest that lymph node dissection should be performed in cases with a predictive score >1.69 but can be omitted in cases with a score ≤1.69.

In this study, we showed that LNM is not an independent risk factor for the DFS or OS. However, this study had several limitations, including its retrospective design, the small number of subjects, and the lack of data on certain pathologic variables (especially the Ki-67 indices and mitotic rates) for all patients. The number of examined lymph nodes was not sufficient, and data on the number of positive lymph nodes were not available for all N+ PNETs. We, therefore, cannot explain the relationship between the lymph node positivity ratio (number positive/examined

Table 4 Risk model of the factors affecting LNM in patients with PNET (*n* = 83)

	n	Univariate analysis			Multivariate analysis		
		OR (95% CI)	*P* value	Estimate	OR (95% CI)	*P* value	Estimate
Age (years)							
>57	41	1.20 (0.41–3.48)	0.740	0.18	1.30 (0.40–4.19)	0.660	0.26
≤57	42						
Tumor size (cm)							
>1.8	38	5.33 (1.56–18.1)	0.008	1.67	4.14 (1.15–14.9)	0.030	1.42
≤1.8	45						
Location of primary tumor							
Ph	27	4.12 (1.35–12.5)	0.013	1.42	2.69 (0.82–8.82)	0.100	0.99
Pb, Pt	56						
Functional PNET							
No	62	0.17 (0.63–14.5)	0.170	1.11	2.03 (0.38–10.8)	0.410	0.71
Yes	21						

CI confidence interval, *LNM* lymph node metastasis, *OR* odds ratio, *PNET* pancreatic neuroendocrine tumor

Predictive score = 0.26 × (Age > 57 years) + 1.42 × (Tumor size > 1.8 cm) + 0.99 × (Ph location) + 0.71 × (Non-functional)
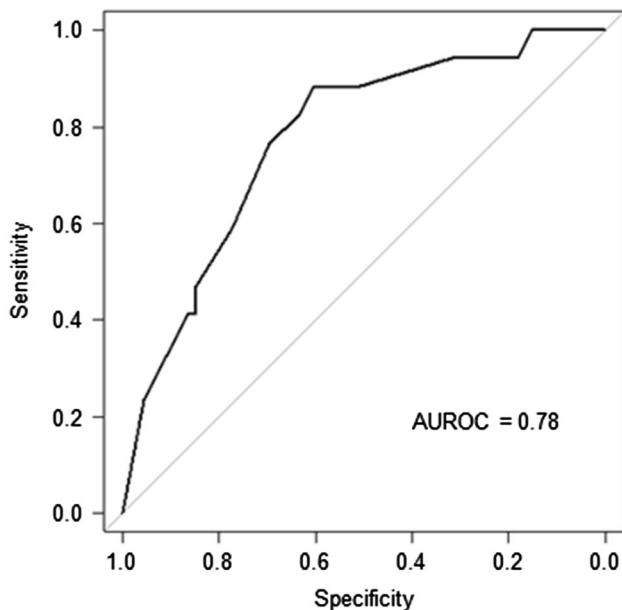

Fig. 2 Receiver-operating characteristic (ROC) curve by lymph node metastasis (LNM). The cut-off value was 1.69 (sensitivity: 0.88 and specificity: 0.61). *AUROC* area under the receiver-operating characteristic curve (0.78)

number) and the survival. Further research regarding advanced PNET is needed [26–28].

In conclusion, we clarified that LNM was not an independent prognostic factor for the DFS or OS. Lymph node dissection is recommended for patients whose predictive score is larger than 1.69.

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