Xu-Feng Zhang ORCID iD: 0000-0002-4483-7326

Flavio Rocha ORCID iD: 0000-0002-6257-5796

Timothy Pawlik ORCID iD: 0000-0002-7994-9870

Impact of Tumor Size and Nodal Status on Recurrence of Non-functional Pancreatic Neuroendocrine Tumors ≤2 cm after Curative Resection: A Multi-institutional Study of 392 Cases

Authors: Ding-Hui Dong MD[1*]; Xu-Feng Zhang MD, PhD[1,2*]; George Poultsides MD[4]; Flavio Rocha MD[5]; Sharon Weber MD[6]; Ryan Fields MD[7]; Kamran Idrees MD[8]; Cliff Cho MD[9]; Shishir K Maithel MD[3]; Timothy M. Pawlik MD, MPH, PhD[2], and other members of the U.S. Neuroendocrine Tumor Study Group

Affiliations:

[1] Department of Hepatobiliary Surgery and Institute of Advanced Surgical Technology and Engineering, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[2]Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio

[3] Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, Georgia

[4]Department of Surgery, Stanford University, Palo Alto, California

[5]Department of Surgery, Virginia Mason Medical Center, Seattle, Washington

[6] Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

[7] Department of Surgery, Washington University School of Medicine, St. Louis, Wisconsin

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[8]Division of Surgical Oncology, Department of Surgery, Vanderbilt University, Nashville, Tennessee

[9] Division of Hepatopancreatobiliary and Advanced Gastrointestinal Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan

* These authors contributed equally to the work.

Corresponding Author:

Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.)

Professor and Chair, Department of Surgery

The Urban Meyer III and Shelley Meyer Chair for Cancer Research

Professor of Surgery, Oncology, Health Services Management and Policy

The Ohio State University, Wexner Medical Center

395 W. 12th Ave., Suite 670

614 293 8701 phone

614 293 4063 fax

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Synopsis for Table of Contents: Patients with NF-pNET had a 2-fold increased incidence of LNM if the tumor measured 1.5-2 cm versus <1.5 cm. LNM was associated with a 3-fold increased risk of tumor recurrence after curative resection and a worse RFS versus patients who had no nodal disease after surgery. Surgery for NF-pNETs should be performed among patients with a tumor size ≥1.5 cm because of the relatively high incidence of LNM.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Background: The current study sought to define the impact of lymph node metastasis (LNM) relative to tumor size on tumor recurrence after curative resection for non-functional pancreatic neuroendocrine tumors (NF-pNETs) ≤2 cm.

Methods: Patients who underwent curative resection for ≤2-cm NF-pNETs were identified from a multi-institutional database. Risk factors associated with tumor recurrence, as well as LNM were identified. Recurrence-free survival (RFS) was compared among patients with or without LNM.

Results: A total of 392 ≤2-cm NF-pNETs patients were identified. Among the 328 patients who had lymph node dissection and evaluation, 42 (12.8%) patients had LNM. LNM was associated with tumor recurrence (HR 3.06, p=0.026) after surgery. RFS was worse among LNM versus no LNM patients (5-year RFS, 81.7% vs. 94.1%; p=0.019). Patients with tumors measuring 1.5-2 cm had a 2-fold increase in incidence of LNM versus patients with tumors <1.5 cm (17.9% vs. 8.7%, OR 2.59, p=0.022), as well as a higher risk of advance tumor grade and higher Ki-67 levels (both p<0.01). After curative resection, a total of 14 (8.0%) patients with tumor of 1.5-2 cm and 10 (4.5%) patients with tumor <1.5 cm developed tumor recurrence.

Conclusions: Surgical resection with lymphadenectomy should be considered for patients with NF-pNETs ≥1.5-2.0 cm.

Key words: neuroendocrine tumor; pancreas; surgery; tumor size; lymph node metastasis

Introduction

Pancreatic neuroendocrine tumors (pNETs) are a collection of rare neoplasms with a wide variety of biologic aggressiveness. The incidence of pNETs has increased

over the past few decades with an almost doubling in the identification of these tumors concurrent with improvements in cross-sectional imaging.[1-3] Based on symptoms and hormone secretion, pNETs are generally classified as functional (F-pNETs) versus non-functional pNETs (NF-pNETs) with the majority of tumors (65-90%) being classified in the latter group.[4,5] The lack of early symptoms among patients with NF-pNETs often leads to late discovery, more advanced stage at diagnosis, and worse long-term outcomes compared with patients who have F-pNETs.[6-8]

According to the European Neuroendocrine Tumor Society (ENETS) and American Joint Committee on Cancer (AJCC) 8th Edition staging manual guidelines, surgical resection is recommended for NF-pNETs >2 cm.[9,10] The management of patients with NF-pNETs ≤2 cm is, however, more controversial. Due to the relatively low tendency to progress, as well as the potential morbidity associated with pancreatic resection, some investigators have advocated for observation and surveillance of NF-pNETs ≤2 cm as the preferred management strategy.[11-13] Other experts, however, have highlighted the potential for malignant differentiation, lymph node metastasis (LNM) and distant metastasis even among patients with small NF-pNETs and therefore have argued for resection.[14-16] The topic is particularly important given that the incidence of NF-pNETs ≤2 cm in the United States has increased dramatically over the past two decades with the proportion of patients with NF-pNETs ≤2 cm increasing from 12.3% in 1988 to 20.2% in 2009.[17]

Currently both the ENETS and the National Comprehensive Cancer Network (NCCN) recommend an individualized treatment strategy for small NF-pNETs that may involve resection or observation as dictated by clinical judgement, as well as

patient risk and preference.[9,18] As such, the optimal treatment strategy of small NF-pNETs remains uncertain, and the guidelines are often unclear and not applicable to a "real life" setting.[19] In addition, as minimally invasive techniques have expanded, more and more surgeons have adopted surgical resection for pNETs regardless of lesion size.[17,20,21] Most previous data have focused on tumor size and LNM as risk factors associated with long-term outcomes following resection of pNETs.[4,5,21,22] In contrast, the incidence of LNM relative to tumor size on prognosis among patients with NF-pNETs ≤2 cm has not been well defined. Therefore, the objective of the current study was to define the impact of tumor size on risk of LNM, as well as characterize the association of tumor size and LNM among patients undergoing curative-intent resection for small NF-pNETs ≤2 cm.

Methods

Study cohort

Patients who underwent surgical resection for pNETs between 1997 and 2016 were identified from the US Neuroendocrine Tumor Study Group.[23] Inclusion criteria for the current study were patients with: (1) non-functional tumor; (2) largest tumor diameter ≤ 2 cm; (3) curative-intent resection (R0/R1). Exclusion criteria included: (1) presence of distant metastasis; (2) death within 90-days after operation; (3) cytoreductive or palliative (R2) resection. NF-pNETs were defined as asymptomatic if the tumor had no evidence of hormone overproduction; patients with no tumor-related hormone function who had symptoms related to tumor expansion and invasiveness, such as abdominal pain, jaundice, weight loss, etc. were still

categorized as NF-pNETs.[10] The study was approved by the Institutional Review Boards at each participating institution.

Data collection

Demographic, clinical and pathologic data at each institution were collected using a standardized datasheet. Tumor size, primary tumor location, the total number of LNs examined (TNLE), the number of LNM, Ki-67, tumor differentiation, perineural invasion, vascular invasion and surgical margin status were determined based on the final pathological report. A minimum margin width of >1 mm was designated as an R0 margin; an R1 margin was defined as the microscopic presence of tumor at the margin or a minimum margin length of ≤1 mm.[24]

Following surgery, each patient was followed regularly with ultrasonography, computed tomography (CT) and/or magnetic resonance imaging (MRI) to monitor for recurrence. Recurrence of NF-pNETs was determined by suspicious imaging finding or biopsy-proven tumor. Recurrence patterns were classified as pancreas-only and distant recurrence. Recurrence-free survival (RFS) was defined as the time from surgical resection to tumor recurrence.

Statistical analysis

Categorical variables were reported as totals and percentages. The $\chi 2$ test or Fisher exact test was used for comparison, as appropriated. Continuous variables were expressed as median with interquartile ranges (IQRs) and compared using the Mann-Whitney U test. Kaplan-Meier survive curves were plotted and compared using the log-rank test. Cox-proportional hazard regression models were used to identify

risk factors associated with RFS on univariate and multivariable analyses; results were reported as hazard ratios (HRs) and 95% confidence intervals (95% CI). Logistic regression models were used to identify factors associated with LNM with results as odds ratio (OR) and 95% CI. A *P*-value <0.05 (two-tailed) was considered statistically significant for all analyses. Statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA).

Results

Baseline Characteristics

Among 989 patients who underwent curative-intent resection for NF-pNETs, a total of 392 (39.6%) patients had a primary tumor ≤2 cm and comprised the analytic cohort (**Table1**). Median age was 59 (IQR 50–66) years, and roughly half of the cohort was female (n=204, 52.0%). A majority of patients had no genetic syndrome (n=349, 89.3%), and more than one-half of patients were diagnosed incidentally without any antecedent symptoms (n=213, 54.3%). Given that most NF-pNETs were located in the pancreatic tail (n=175, 44.6%), the most common procedure was a distal pancreatectomy (n=237, 60.5%). Median operative time was 235 (IQR 190-315) minutes with a median estimated blood loss of 200 (IQR 50-300) ml. In the post-operative period, 227 (58.1%) patients had at least one complication; roughly one-third of these patients (n=87, 38.5%) experienced a Clavien-Dindo III-IV complication. On final pathology, most tumors were well-differentiated (n=325, 92.6%) and had a low ki-67 < 3% (n=207, 73.4%). R0 resection was achieved in the overwhelming majority of patients (n=354, 90.5%).

Lymph node metastasis and tumor recurrence

After a median follow-up of 33.7 (IQR 12.0-59.4) months, only 24 (6.1%) patients experienced tumor recurrence. The 3-, 5-, and 10-year RFS for the entire cohort was 95.1%, 91.9% and 75.1%, respectively. On univariate analysis, only LNM was associated with tumor recurrence (HR 3.06, 95% CI 1.15-8.17, *p*=0.026)(**Table 2**). Among the 328 patients who had a lymph node dissection, the incidence of LNM was 12.8% (n=42) with the vast majority of patients having node negative disease (n= 286, 87.2%). Perhaps not surprisingly, patients with LNM were more likely to have an associated genetic syndrome, high Ki-67, as well as perineural invasion compared with patients who had node negative disease (**Table 1**). RFS among patients with LNM was worse compared with patients who had node negative disease (5-year RFS, LNM 81.7% vs. node negative 94.1%; *p*=0.019)(**Figure 1**).

Tumor size and nodal metastasis

On multivariable analysis, tumor size (1.5-2.0 cm vs. <1.5 cm, OR 2.59, 95% CI 1.15-5.83, *p*=0.022) and Ki-67 category (≥3% vs. <3%, OR 2.20, 95% CI 1.02-4.78, *p*=0.045) were independently associated with risk of LNM (**Table 3**). Specifically, the incidence of LNM was almost two-fold higher among patients with 1.5-2 cm NF-pNETs (n=145) versus <1.5 cm NF-pNETs (n=183) (LNM, 1.5-2 cm 17.9% vs. <1.5 cm 8.7%)(OR 2.28, 95% CI 1.17-4.44, *p*=0.015)(**Figure 2a**), although TNLE and number of LNM were no different among patients with 1.5-2 cm NF-pNETs versus <1.5 cm NF-pNETs (TNLE, median 9 vs. 8, *p*=0.734; number of LNM, median 2 vs. 1.5, *p*=0.287)(**Figure 2b and c**).

In addition to a higher incidence of LNM, 1.5-2 cm NF-pNETs were associated with more advanced disease including a Ki-67 ≥3% (1.5-2 cm 35.9% vs. <1.5 cm 18.8%; *p*=0.001), as well as worse WHO tumor grade (G2 grade, 1.5-2 cm 29.2% vs. <1.5 cm 13.9%; *p*=0.001) versus patients with a NF-pNETs <1.5 cm (**Table 4**). Of note, after curative resection, a total of 14 (8.0%) patients with tumors 1.5-2 cm and 10 (4.5%) patients with a tumor <1.5 cm developed tumor recurrence. RFS was no different among patients with NF-pNETs that measured 1.5-2 cm versus NF-pNETs <1.5 cm (5-year RFS, 1.5-2 cm 87.3% vs. <1.5 cm 95.6%; *p*=0.131)(**Figure 3a**). In addition, recurrence patterns were no different among patients with NF-pNETs of 1.5-2 cm and NF-pNETs <1.5 cm (distant recurrence, 64.3% vs. 50.0%, *p*=0.484)(**Figure 3b**).

Discussion

The treatment strategy for small NF-pNETs (≤2 cm) remains controversial, as both surgical resection and observation are recommended according to various guidelines.[10,16] One of the main challenges in the management of small NF-pNETs is accurate assessment of the natural history of the disease, as well as the ability to predict the risk of LNM and long-term outcomes. The clinical course of NF-pNETs ≤2 cm has not been well-defined and, therefore, many surgeons often advocate for surveillance of these small tumors.[17,20,21] Given that the general incidence of NF-pNETs is relatively low and most previous studies have been single center series with small sample sizes, data on NF-pNETs <2 cm remain scarce. The current study was important because it demonstrated that roughly 40% of patients who underwent curative resection for NF-pNETs at one of several large HPB centers had a tumor size ≤2 cm. Of note, patients with a small NF-pNET had a 2-fold increased incidence of

LNM if the tumor measured 1.5-2 cm versus <1.5 cm (17.9% vs. 8.7%, *p*=0.015). Furthermore, LNM were present among 12.8% of patients with a NF-pNET ≤2 cm. In turn, LNM was associated with a 3-fold increased risk of tumor recurrence after curative resection and a worse RFS versus patients who had no nodal disease after surgery (5-year RFS, nodal positive 81.7% vs. nodal negative 94.1%; *p*=0.019). Collectively, the data strongly suggest that surgery for NF-pNETs should be performed among patients with a tumor size ≥1.5 cm because of the relatively high incidence of LNM.

Some investigators have proposed that surveillance of NF-pNETs ≤2 cm is safe, as most of these tumors grow very slowly with no disease-related death among patients undergoing active surveillance.[12,13] Data from two meta-analyses demonstrated that pNET tumor growth was observed in 50% of patients with small NF-pNET ≤2 cm; in addition, 9% of patients developed metastasis during surveillance.[12,13] In a separate study of patients with NF-pNETs ≤2 cm derived from the National Cancer Data Base (NCDB), the authors reported a 5-year overall non-disease specific survival of 27.6% among patients who did not undergo surgery compared with a 5-year survival of 82.2% among patients who underwent curative-intent resection.[15] In the current study that examined surgical patients exclusively, RFS of 3- and 5-year RFS were 95.1% and 91.9%, respectively. Data from the current data were, therefore, more optimistic about disease specific prognosis for patients with small NF-pNETs ≤ 2 cm. Specifically, compared with the 5-year mortality of 18% reported in the NCDB study, we noted 5-year recurrence to be only about 8% of patients following resection of small pNETs. Our data were more consistent with the expected good prognosis of this patient population and likely

reflected that the previous NCDB study captured all-cause mortality events, which included deaths not related to pNETs. In the current study, 5-year RFS among patients with NF-pNETs <1.5 (95.6%) tended to be better than the prognosis of patients with NF-pNETs measuring 1.5-2 cm (87.3%). In an earlier study by Zhang et al., the authors reported that surgical resection had the most long-term benefit among patients with pNETs ≥1.5 cm, while resection failed to demonstrate a difference in survival compared with surveillance among individuals with tumors <1.5 cm.[25] Taken together, patients with NF-pNETs measuring 1.5-2 cm should be strongly considered for surgical resection, whereas patients with tumor <1.5 cm may be more appropriate candidates for surveillance.

While patients with small NF-pNET generally had a good prognosis, several factors were associated with a worse long-term survival including tumor size, grade and LNM. In particular, tumor size (1.5-2 cm vs. <1.5 cm) was linked with a higher Ki-67 level, as well as more advanced WHO grade (**Table 3**). Jung et al. had similarly reported that patients with tumor measuring 1.5-2 cm had a higher likelihood to be WHO G2/G3 tumors versus tumors <1.5 cm.[26] Tumor size, therefore, correlated with the potential for the presence of other adverse pathological features. In particular, the risk of recurrence was nearly 2-fold higher among patients with tumors ≥1.5 cm (8.2%) compared with patients who had tumors <1.5 cm (4.5%) – suggesting a subset of patients with NF-pNETs ≤ 2 cm had a more aggressive natural history. Interestingly, among patients who did recur, the pattern of recurrence was no different comparing patients with tumor NF-pNET <1.5 cm versus ≥1.5 cm.

The presence of LNM was particularly associated an increased risk of tumor recurrence (**Table 2**). The need for routine performance of lymphadenectomy at the

time of resection for NF-pNETs ≤ 2 cm is, however, somewhat controversial.[5,15,17,21,27] National Cancer Center Network guidelines recommend regional lymph node evaluation at the time of resection for NF-pNETs, irrespective of tumor size.[9,18] Despite this, some clinicians have suggested that enucleation of smaller pNETs without nodal evaluation may be acceptable.[15,28] Our group previously reported that regional lymphadenectomy of at least 8 lymph nodes was necessary to stage patients with pNETs accurately.[23] In the current study, the median TNLE were 8 and 9 among patients with pNETs <1.5 cm and 1.5-2.0 cm, respectively (**Figure 2b and c**), suggesting that roughly half of patients had an adequate number of LNs examined. Data on nodal disease is important as the presence of LNM renders the disease stage III regardless of tumor size both in the AJCC and ENETS staging systems.[10,29-32] In the current study, LNM was noted in more than 1 in 10 patients (12.8%) who had a NF-pNET ≤2 cm. In particular, patients with a NF-pNET measuring 1.5 to 2 cm had a 2-fold increased risk of LNM compared with patients who had a NF-pNET <1.5 cm (17.9% vs. 8.7%). Several previous reports had similarly suggested a strong relationship between tumor size and risk of LNM.[17,20,33] For example, Kuo et al. reported a LNM incidence of 36% among patients with a pNET tumor measuring 16-20 mm versus 54% among patients with pNETs measuring and or >20 mm.[17] Therefore, small pNET tumor size does not necessarily preclude the risk of metastasis to the regional nodal basin.[15,17] In turn, patients with small NF-pNETs measuring >1.5 cm should undergo formal lymphadenectomy at the time of resection.

Several limitations should be considered when interpreting data in the current study. While the multi-institutional nature of the study undoubtedly increased the

sample size, as well as the "real-world" application and generalizability of the data, there likely were some inconsistencies in patient selection for surgery, surgical techniques, as well as postoperative surveillance. There were also no patients with G3 ≤2 cm tumors, which was not surprising as these patients are generally not considered for surgical management and should be treated with systemic therapy.[34] In addition, only patients undergoing curative-intent resection for pNETs were included in the analytic cohort. As such, there was no observation / surveillance group that consisted of patients with small NF-pNETs to serve as a comparator to assess the "true" benefit of surgery. The purpose of the study, however, was to determine the incidence and risk factors of LNM, as well as outcomes of patients with small NF-pNETs who underwent surgery.

In conclusion, assessing a large, US multi-institutional national cohort of patients with pNETs, roughly two out of every five patients who underwent curative-intent resection had a tumor ≤2 cm. Among patients undergoing surgical resection for small NF-pNETs, more than 1 in 10 patients had LNM. Patients with tumor of 1.5-2 cm had a 2-fold increase in incidence of LNM versus patients with tumor <1.5 cm, as well as a higher risk of advance tumor grade and higher Ki-67 levels. The presence of LNM was independently associated with a worse long-term RFS. While some previous studies have suggested that pNETs <2 cm are simply safe to follow, [17,20,21] data from the current study strongly suggest that surgical resection with lymphadenectomy should be considered for patients with NF-pNETs ≥1.5-2.0 cm.

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Figure

Figure 1: Recurrence-free survival of patients with or without lymph nodal metastasis (LNM) in the whole cohort (n=392).

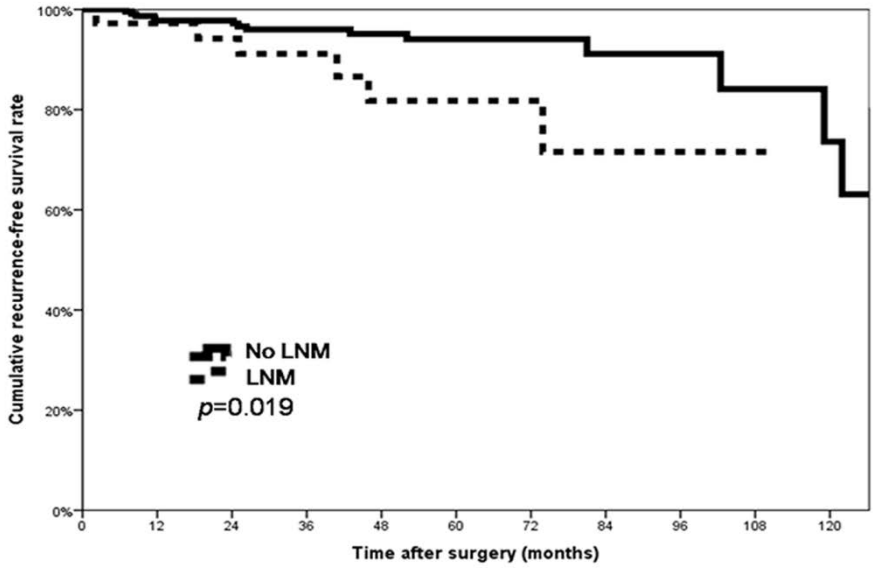


Figure 2: a, Incidence of lymph node metastasis (LNM) among patients with tumor <1.5 cm versus patients with tumor of 1.5-2 cm. The total number of lymph nodes examined (**b**) and number of LNM (**c**) of each patient in the two differently sized tumor groups.

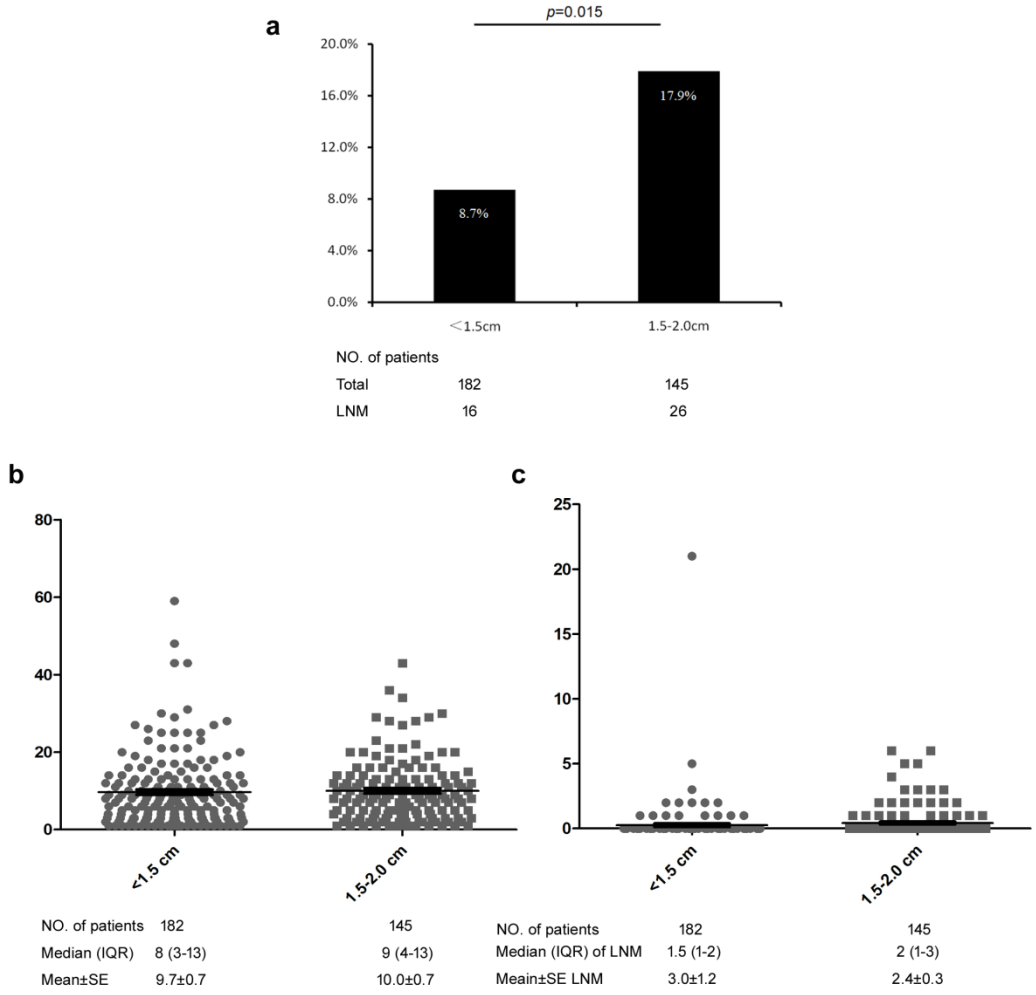
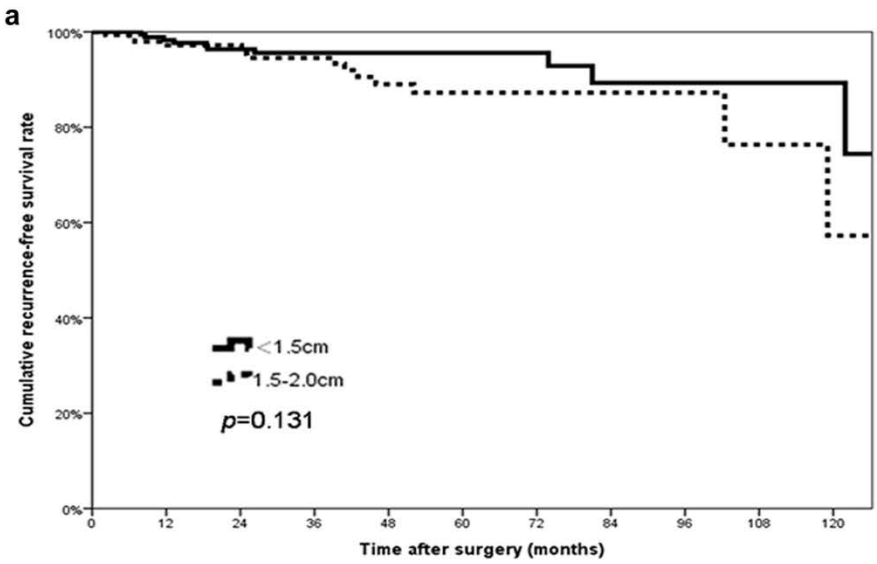
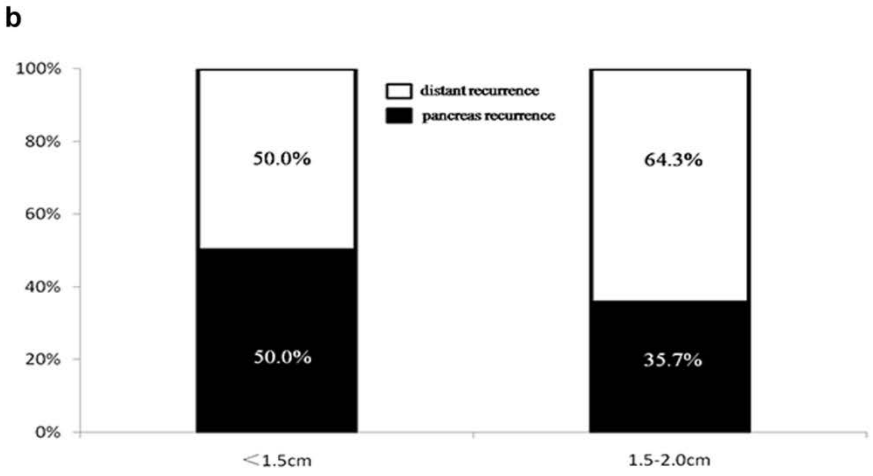


Figure 3: a, Recurrence-free survival of patients with different tumor size (<1.5 cm, n=221 vs. 1.5-2 cm, n=171); **b**, Recurrence patterns among patients with tumor <1.5 cm versus patients with tumor of 1.5-2 cm after curative resection.





No. of recurrence	10	14
pancreas-only	5	5
distant	5	9

Table 1: Clinical and pathological characteristics of the study cohort with NF-pNETs ≤2.0 cm

Variables	Overall (n=392)	LNM (n=42)	No LNM (n=286)	*p* value
Age (years)	59 (50-66)	55 (46-65)	60 (50-66)	0.288
Sex				0.841
Female	204 (52.0%)	20 (47.6%)	150 (52.4%)	
Male	188 (48.0%)	22 (52.4%)	136 (47.6%)	
Genetic syndrome				0.004
None	349 (89.3%)	29 (69.0%)	259 (90.9%)	
MEN-1	37 (9.5%)	12 (28.6%)	23 (8.1%)	
VHL	4 (1.0%)	1 (2.4%)	3 (1.1%)	
Symptomatic				0.079
N0	213 (54.3%)	16 (38.1%)	162 (56.6%)	
Yes	179 (45.7%)	26 (61.9%)	124 (43.4%)	
Primary location				0.000
Head	95 (24.2%)	26 (61.9%)	61 (21.3%)	

Uncinated	15 (3.8%)	1 (2.4%)	10 (3.5%)	
Neck	28 (7.1%)	3 (7.1%)	21 (7.3%)	
Body	79 (20.2%)	1 (2.4%)	60 (21.0%)	
Tail	175 (44.6%)	11 (26.2%)	134 (46.9%)	
Ki-67 category				0.022
<3%	207 (73.4%)	17 (51.5%)	155 (74.2%)	
≥3%	75 (26.6%)	16 (48.5%)	54 (25.8%)	
Tumor differentiation				0.791
Well	325 (92.6%)	34 (89.5%)	236 (92.2%)	
Moderately	26 (7.4%)	4 (10.5%)	20 (7.8%)	
Surgical technique				0.006
Open	278 (70.9%)	39 (92.9%)	197 (68.9%)	
Laparoscopic/robotic	114 (29.1%)	3 (7.1%)	89 (31.1%)	
Type of resection				0.000
Enucleation	39 (9.9%)	4 (9.5%)	11 (3.8%)	
Classic PD	36 (9.2%)	10 (23.8%)	25 (8.7%)	

Pylorus preserving PD	52 (13.3%)	14 (33.3%)	38 (13.3%)	
Central pancreatectomy	24 (6.1%)	1 (2.4%)	11 (3.8%)	
Distal pancreatectomy	237 (60.5%)	12 (28.6%)	198 (69.2%)	
Total pancreatectomy	4 (1.0%)	1 (2.4%)	3 (1.0%)	
Perineural invasion	40 (13.3%)	12 (37.5%)	26 (11.9%)	0.000
Major vascular resection	5(1.3%)	2(4.9%)	2(0.7%)	0.083
Operation time (min)	235(190-315)	256(214-345)	240(195-320)	0.286
Blood loss (ml)	200 (50-300)	300 (200-800)	200 (50-300)	0.012
Margin status				0.008
R0	354 (90.5%)	32 (78.0%)	266 (93.0%)	
R1	37 (9.5%)	9 (22.0%)	20 (7.0%)	
Postoperative morbidity	227 (58.1%)	24 (57.1%)	161 (56.5%)	0.920
Severe complication (III-IV)	87 (38.5%)	12 (50.0%)	61 (37.9%)	0.515

Table 2: Risk factors of tumor recurrence after curative resection for NF-pNETs ≤2 cm

Variable	Univariate analysis	
	HR (95% CI)	*p* value
Gender(F/M)	0.75 (0.33-1.71)	0.487
Age(<65/≥65)	0.40 (0.12-1.35)	0.140
Symptomatic	1.71 (0.76-3.85)	0.198
Ki-67 category		0.538
<3%	Ref.	
≥3%	1.34 (0.53-3.43)	
WHO grade		0.426
G1	Ref.	
G2	1.52 (0.54-4.27)	
Tumor differentiation		0.757
Well	Ref.	
Moderately	1.26 (0.29-5.54)	
Tumor size (cm)		0.137
<1.5	Ref.	
1.5-2	1.85 (0.82-4.18)	
Lymph nodes metastasis	3.06 (1.15-8.17)	0.026
Perineural invasion	1.19 (0.34-4.17)	0.783
Lymphvascular invasion	2.03 (0.73-5.61)	0.175
Final resection status		
R0	Ref.	0.859
R1	1.12 (0.33-3.78)	

Table 3: Risk factors of lymph node metastasis for NF-pNETs ≤2 cm

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender (F/M)	1.21 (0.63-2.32)	0.559		
Age (<65/≥65)	0.74 (0.35-1.57)	0.432		
Functional status	0.85 (0.10-6.91)	0.877		
Symptomatic	2.12 (1.09-3.13)	0.027		
CgA (≤160/＞160ng/L)	3.08 (0.91-10.37)	0.070		
Ki-67 category				
<3%	Ref.	0.009	Ref.	0.045
≥3%	2.70 (1.28-5.72)		2.20 (1.02-4.78)	
Tumor differentiation				
Well	Ref.	0.570		
Moderately	1.39 (0.45-4.31)			
WHO grade				
G1	Ref.	0.133		

G2	1.83 (0.83-4.03)			
Tumor size (cm)		0.015		0.022
<1.5	Ref.		Ref.	
1.5-2	2.28 (1.17-4.44)		2.59 (1.15-5.83)	

Table 4: Clinical and pathological characteristics of patients with NF-pNETs <1.5 cm and NF-pNETs of 1.5-2.0 cm

Variables	<1.5 cm (n=221)	1.5-2.0 cm (n=171)	*p* value
Age (years)	59(50-66)	59(50-67)	0.119
Sex			0.416
Female	119 (53.8%)	85 (49.7.%)	
Male	102 (46.2%)	86 (50.3%)	
Genetic syndrome			0.323
None	201 (91.0%)	148 (87.1%)	
MEN-1	19 (8.6%)	18 (10.6%)	
VHL	1 (0.5%)	3 (1.8%)	

Symptomatic			0.098
No	112 (50.7%)	101 (59.1%)	
Yes	109 (49.3%)	70 (40.9%)	
Primary location			0.072
Head	54 (24.4%)	41 (24.0%)	
Uncinated	9 (4.1%)	6 (3.5%)	
Neck	13 (5.9%)	15 (8.8%)	
Body	55 (24.9%)	24 (14.0%)	
Tail	90 (40.7%)	85 (49.7%)	
Ki-67 category			0.001
＜3%	125 (81.2%)	82 (64.1%)	
＞3%	29 (18.8%)	46 (35.9%)	
Tumor differentiation			0.064
Well	186 (94.9%)	139 (89.7%)	
Moderately	10 (5.1%)	16 (10.3%)	
WHO grade			0.001

G1	149 (86.1%)	97 (70.8%)	
G2	24 (13.9%)	40 (29.2%)	
Lymph nodes metastasis	16 (8.7%)	26 (17.9%)	0.013
Surgical technique			0.064
Open	165 (74.7%)	113 (66.1%)	
Laparoscopic/robotic	56 (25.3%)	58 (33.9%)	
Type of resection			0.571
Enucleation	21 (9.5%)	18 (10.5%)	
Classic PD	16 (7.2%)	20 (11.7%)	
Pylorus preserving PD	32 (14.5%)	20 (11.7%)	
Centralpancreatectomy	16 (7.2%)	8 (4.7%)	
Distal pancreatectomy	134 (60.6%)	103 (60.2%)	
Total pancreatectomy	2 (0.9%)	2 (1.2%)	
Perineural invasion	24 (14.0%)	16 (12.4%)	0.681
Major vascular resection	3 (1.4%)	2 (1.2%)	0.877
Lymphadenectomy	183 (82.8%)	145 (84.8%)	0.584

Operation time (min)	235 (184-311)	220 (189-304)	0.253
Blood loss (ml)	200 (100-350)	200 (100-300)	0.004
Margin status			0.505
R0	202 (91.4%)	152 (89.4%)	
R1	19 (8.6%)	18 (10.6%)	
Postoperative morbidity	126 (57.3%)	101 (59.1%)	0.722
Severe complication (III-V)	53 (41.7%)	34 (34.3%)	0.257