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Analysis of recurrence after resection of well-differentiated non-functioning pancreatic neuroendocrine tumors

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Abstract

Although pancreatic neuroendocrine tumors (PNETs) are generally considered to have a favorable overall prognosis after resection, disease recurrence has been observed. Few studies have specifically addressed recurrence after resection of PNETs, especially for non-functioning PNETs (NF-PNETs). The aim of our study is to analyze the recurrence of resected well-differentiated NF-PNETs.

Patients who underwent surgical resection for grade 1 and 2 NF-PNETs without synchronous metastasis were identified for analysis. Patients were treated from January 2009 to December 2017 in our institution. Univariate and multivariate cox regression analysis were conducted to identify prognostic factors.

Of the 88 patients, 46 were men (52%) and the mean age was 52 years. With a median follow-up of 49.1 months (range, 8–122 months), there were 12 recurrences (14%). Liver was the most common recurrence site (7/12, 58%). The 1-, 3-, and 5-year recurrence-free survival was 99%, 90%, and 88%, respectively. Univariate analysis identified that age >52 years, positive lymph nodes, tumor grade 2, and Ki67 index ≥5% were statistically significant. Multivariate analysis identified that Ki67 index ≥5% (hazard ratio [HR], 4.69; 95% confidence interval [CI], 1.36–16.75, $P = .015$), positive lymph nodes (HR, 6.75; 95% CI, 1.73–24.43, $P = .006$) were independently associated with recurrence. The 5-year disease-free survival rate was 53% (95% CI, 14.20–91.81%) for patients with Ki-67 ≥5% or (and) positive lymph nodes, while 95% (95% CI, 82.26–100%) for the patients without these 2 factors.

Ki67 index and lymph node status are independently associated with recurrence after resection of well-differentiated NF-PNETs in this study.

Abbreviations: CI = confidence interval, ENETS = European Neuroendocrine Tumor Society, HR = hazard ratio, ISGPS = International Study Group of Pancreatic Surgery, NCCN = National Comprehensive Cancer Network, NF-PNETs = non-functioning pancreatic neuroendocrine tumors, PNETs = pancreatic neuroendocrine tumors, WHO = World Health Organization.

Keywords: nonfunctional pancreatic neuroendocrine tumors, pancreatic neuroendocrine tumors, recurrence

1. Introduction

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors with variable clinical behavior.[1] In recent years, with the widespread use of high-quality imaging techniques, the incidence of pancreatic neuroendocrine tumors (PNETs) has increased, especially for non-functioning pancreatic neuroendocrine tumors (NF-PNETs).[2] As a type of neoplasm with malignant potential, predictors for PNETs have been studied extensively. Tumor grade, tumor size, vascular invasion, perineural invasion, lymph node involvement, and distant metastasis have been reported to be associated with survival.[3–6] However, few studies have specifically addressed factors associated with recurrence after resection.

Although pancreatic neuroendocrine tumors are generally considered to have a good overall prognosis after resection, disease recurrence has been observed in 21% to 42% of patients with PNETs.[7] As for well-differentiated NF-PNETs (grade 1 and 2), the recurrence rate is reported to be 17% after resection.[8] Distant metastasis has been reported as the most common pattern of recurrence, leading to a poor survival of these patients.[8–10] However, there have been few reports regarding the recurrence after resection of PNETs, especially for NF-PNETs. Furthermore, most studies analyzing the factors associated with recurrence of resected PNETs included the patients with insulinoma, Zollinger–Ellison, metastases or locally advanced disease. All these

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Q-qT and XW have contributed equally to this work and therefore shared first authors.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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patients have a different prognosis. As reported by Rindi et al,[11] the tumor-related death of insulinoma, NF-PNETs, and other types of PNETs are 4.9%, 22.1%, and 25.7%, respectively. In addition, the WHO grade 3 and synchronous metastasis are widely regarded as predictors of aggressive biological behavior and poor survival in patients with PNETs.[2,12]

Therefore, the aim of our study is to assess the recurrence rate and patterns of resected grade 1 and 2 NF-PNETs without synchronous metastasis and evaluates the factors associated with recurrence.

2. Methods

We retrospectively analyzed the patients who underwent resection for PNETs from January 2009 to December 2017 in our institution. This study was approved by the Institutional Ethic Committee of West China Hospital, Sichuan University. Nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) were defined as PNETs without clinical symptoms of hormone hypersecretion. Eighty-eight patients with well-differentiated NF-PNETs (grade 1 and 2) and without synchronous metastasis were selected. Patients with multiple endocrine neoplasia or von Hippel-Lindau and those with endocrine tumors arising from the papilla of Vater, bile duct, or duodenum were excluded. Data points including age, sex, presentation, and type of resection were retrieved from medical records. Postoperative pancreatic fistulae were defined according to the International Study Group of Pancreatic Surgery (ISGPS)[13] and complications were classified using the Clavien-Dindo system.[14] Pathology results were reviewed: tumor location, tumor size, vascular invasion, resection margin, positive Lymph nodes, TNM stage, and Ki67 index. Tumors were classified according to the 2010 WHO grading system.[11] Grades were defined as follows: low grade (G1), Ki-67 index <3%; intermediate grade (G2), 3% to 20% Ki-67 index.

Follow-up was performed every 6 months in the first year and annually thereafter. The follow-up program consisted of physical examination, laboratory tests, and radiological imaging. Recurrence-free survival was defined as the percentage of patients without recurrence after resection. Patients who were lost at follow-up or did not receive follow-up at our institution were exclude from the survival analysis.

Univariate and multivariate cox regression analysis were conducted to identify factors associated with recurrence. Kaplan Meier survival analysis with log rank test was performed to investigate the survival. Statistical difference was considered significant when *P*-value was <.05.

3. Results

Characteristics of 88 patients with resected well-differentiated NF-PNETs are listed in Table 1. There was no sex predominance (men, 46/88, 52%). The mean age was 52 years, ranging from 26 to 75. Of the 88 patients, 48 patients (55%) were symptomatic. Abdominal pain or distension was the most common symptom (37/88, 42%), followed by weight loss, jaundice (4/88, 5%), abdominal mass (2/88, 2%). Gastrointestinal bleeding was caused by tumor invasion of the duodenum. Most patients underwent standard pancreatic resection including pancreaticoduodenectomy (32/88, 36%) and distal pancreatectomy (37/88, 42%). Postoperative complications occurred in 46 patients (52%) and 18 patients (18%) graded III–IV. There was no in-hospital death in our study. Thirty-four patients (37%) had a postoperative pancreatic fistula, of those, 14 patients (16%) graded B and C.

Table 1

Demographics, presentation, type of resection, and postoperative complications of 88 patients with resected well-differentiated NF-PNETs.

Features	N (%)
Sex	
Male	46 (52)
Female	42 (48)
Age (IQR, y)*	51 (44–60)
≤51	38 (43)
>51	50 (57)
Symptom	
Asymptomatic	40 (45)
Symptomatic	48 (55)
Abdominal pain or distension	37 (42)
Weight loss	4 (5)
Jaundice	4 (5)
Abdominal mass	2 (2)
Gastrointestinal bleeding	1 (1)
Surgical procedure	
Pancreatoduodenectomy	32 (36)
Distal pancreatectomy	37 (42)
Enucleation	14 (16)
Central pancreatectomy	2 (2)
Total pancreatectomy	3 (3)
Pancreatic fistula	
Biochemical leak	20 (23)
Grade B	12 (14)
Grade C	2 (2)
Complications (Clavien-Dindo)	
I–II	28 (32)
III–IV	18 (18)

* The values indicated are expressed as the median (IQR), IQR = interquartile range, NF-PNETs = non-functioning pancreatic neuroendocrine tumors.

Table 2 shows the pathological and recurrence features. The greatest number of tumors were located in head (38/88, 43%), followed by 35% located in body and 22% located in tail. The mean size of tumors was 3.7 cm (range, 1.1–9.2 cm). Five patients were confirmed to have vascular invasion. Notably, 13 patients (13/88, 15%) were identified with positive lymph nodes. Fourteen patients (16%) were of stage I, while 41 patients (47%) were of stage II, and 33 patients (38%) were of stage III. Regarding Ki67 index, 32 patients (36%) had Ki67 index <3% (WHO grade 1), and 56 patients (64%) had Ki67 index ≥3% (WHO grade 2). Of the 56 patients with grade 2, 20 patients (23%) had Ki67 index ≥5%. There were 12 recurrences (14%) in total, and 6 patients of these were with positive lymph nodes, 10 patients with tumor grade 2. Seven recurrences (7/12, 58%) were located in liver with or without new lymph nodes, 3 located in the pancreatic remnant (local) and 2 located in the lymph nodes only.

Follow-up was achieved in 81 patients (81/88, 92%), of these there were 12 recurrences (14%). Median recurrence-free survival after primary resection was 49.1 months (range, 8–122 months). The 1-, 3-, and 5-year recurrence-free survival was 99%, 90%, and 84%, respectively (Fig. 1). Overall survival for those with and without recurrence was 83% and 97% (*P* = .18). As shown in Table 3, univariate analysis identified that age >52 years, positive lymph nodes, tumor grade 2, and Ki67 index ≥5% were statistically significant while sex, symptoms, tumor location, size, vascular invasion, and resection margin were not.

Table 2

Pathological and recurrence features of 88 patients with resected well-differentiated NF-PNETs.

Features	N (%)
Tumor location	
Head	38 (43)
Body	31 (35)
Tail	19 (22)
Tumor size (IQR, cm)*	3.7 (2.5–4.5)
<2	14 (16)
2–4	43 (49)
>4	31 (35)
Vascular invasion	5 (6)
R1 resection margin	3 (3)
Positive lymph nodes	13 (15)
1–2	7 (8)
3–4	4 (5)
>5	2 (2)
Tumor stage	
I	14 (16)
II	41 (47)
III	33 (38)
Ki-67 index (IQR, %)*	3.9 (1-6)
<3	32 (36)
3–5	36 (41)
≥5	20 (23)
Recurrence	12 (15)
Positive lymph nodes	6 (50)
Ki67 index ≥5%	6 (50)
Located in liver	7 (58)
Ki67 index ≥3%	10 (83)

* The values indicated are expressed as the median (IQR), IQR = interquartile range, NF-PNETs = non-functioning pancreatic neuroendocrine tumors.

Multivariate analysis identified that Ki67 index ≥5% (hazard ratio [HR], 4.69; 95% confidence interval [CI], 1.36–16.75), positive lymph nodes (HR, 6.75; 95% CI, 1.73–24.43) were independently associated with recurrence. The 5-year recurrence-free survival was 53% (95% CI, 14.20–91.81%) with Ki-67 ≥5% or positive lymph nodes and 95% (95% CI, 82.26–100%) for the patients without these 2 factors ($P < .001$; Fig. 2).

4. Discussion

Generally, pancreatic neuroendocrine tumors (PNETs) are considered to have low malignant potential and a good overall prognosis. However, due to their heterogeneity and rarity, the natural history of PNETs is not fully understood and recurrence has been observed after curative resection. Besides, the prognosis of NF-PNETs and other PNETs is different. A large scaled study has reported that functioning-PNETs have different behavior in terms of disease recurrence than NF-PNETs.[10] The recurrence of PNETs including functioning tumors may not reflect that of NF-PNETs. Furthermore, according to the WHO 2010 grading system, grade 3 is classified as poorly differentiated neuroendocrine carcinomas (NECs) and the therapeutic strategy for NECs is different from other PNETs. The same author has demonstrated that patients with grade 1 and 2 have a completely different recurrence pattern than patients with grade 3.[10] Due to the different histologic characteristic and biologic behavior, it is necessary to discriminate grade 1 and 2 from grade 3 when analyzing the recurrence of NF-PNETs.

Although National Comprehensive Cancer Network (NCCN) suggests that patients should be surveyed for 3 to 12 months after resection and thereafter every 6 to 12 months, there is no difference regarding follow-up strategy between low and high

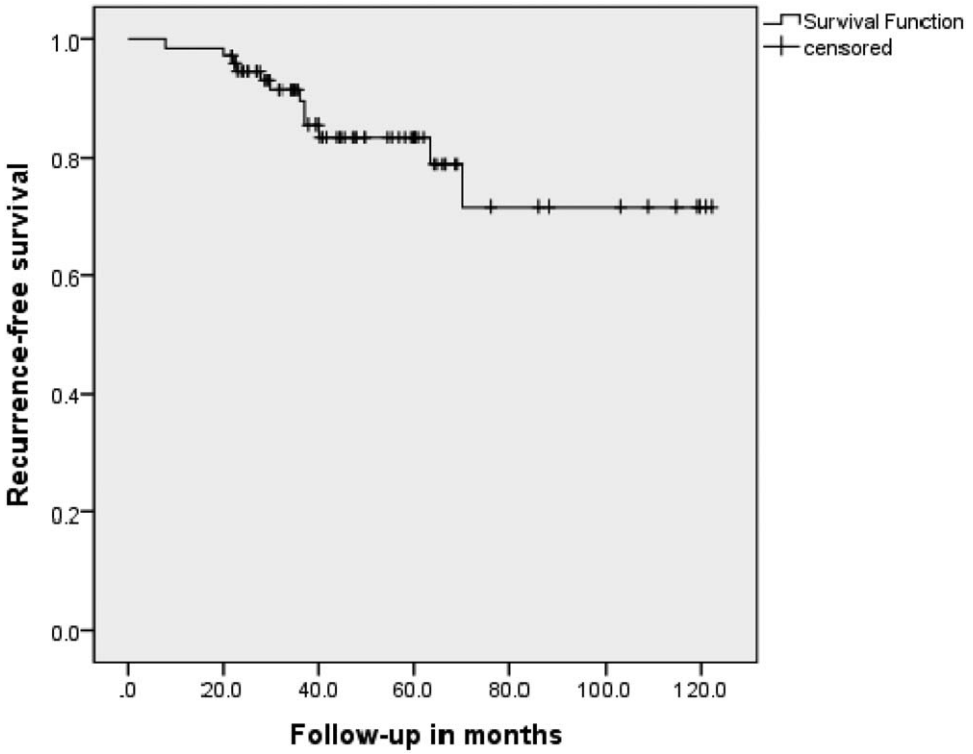

Figure 1. Recurrence-free survival of 81 patients with follow-up.

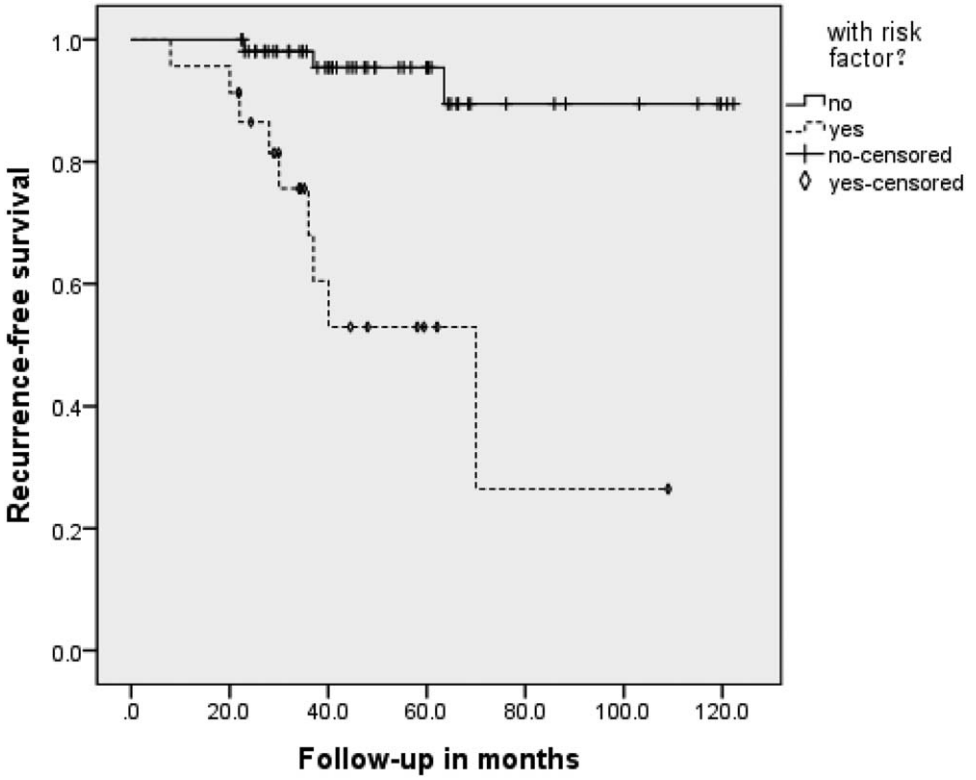

Figure 2. Comparison of recurrence-free survival after resection between patients with Ki-67 ≥5% or (and) positive lymph nodes and those without ($P < .001$).

Table 3

Univariate and multivariate analysis of recurrence-free survival in 81 patients with resected well-differentiated NF-PNETs[*].

		Univariate Cox regression			Multivariate Cox regression		
Feature	**N**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Gender							
Female	41	1.46	0.45–4.80	.528			
Age, y							
>52	45	4.18	3.91–19.33	**.032**	2.98	1.47–21.66	.183
Presence of symptom	46	1.81	0.48–6.83	.350			
Surgical procedure							
Enucleation	11	ref	-	-			
PD	35	2.30	0.59–8.90	.228			
DP	31	1.42	0.47–7.64	.796			
Others[†]	4	0.88	0.08–7.12	.827			
Severe complication[‡]	16	1.61	0.21–12.59	.654			
Tumor location							
Head	34	ref	-	-			
Body	29	2.01	0.50–8.82	.310			
Tail	18	1.90	0.38–9.44	.431			
Tumor size							
<2	12	ref	-	-			
2–4	40	2.34	0.74–8.56	.212			
>4	29	2.65	0.88–9.76	.244			
Vascular invasion	4	2.99	0.26–15.51	.549			
R1 resection margin	3	1.87	0.33–8.45	.485			
Positive lymph nodes	11	11.57	3.52–38.06	**<.001**	6.75	1.73–24.48	**.006**
Ki67 index ≥3% (G2)	53	4.28	1.93–19.60	**.041**			
Ki67 index ≥5%	19	7.23	2.24–23.38	**.001**	4.69	1.36–16.75	**.015**

CI = confidence interval, DP = distal pancreatectomy, HR = hazard ratio, NF-PNETs = non-functioning pancreatic neuroendocrine tumors, PD = pancreatoduodenectomy, 7 patients were lost to follow-up.

[*] Parameters with $P < .05$ in univariate analysis are included in multivariate analysis.

[†] Others include: total pancreatectomy, central pancreatectomy, and duodenum-preserving pancreatic head resection.

[‡] Severe complication include Clavien-Dindo classification III and above.

P values marked as bold are significant.

risk group on the basis of patient characteristics. Additionally, adjuvant treatment after surgical resection is not recommended for patients with NF-PNETs.[2] Our results identified that positive lymph nodes and an elevated Ki67 index were independently associated with recurrence after resection of NF-PNET. Therefore, more frequent follow-up or adjuvant therapy may be needed after surgical resection in these patient groups.

In our study, the incidence of recurrence was 14% with the liver being the most common site (7/12, 58%). This is a relatively low recurrence rate compared with other series of NF-PNETs.[10] Our lower recurrence rate is likely due to the selection of only grade 1 and 2 NF-PNETs for the current analysis. In several published reports, same with us, distant metastases were mostly observed and liver was the most frequent recurrence site.[7,10,15] Although liver metastasis predicting poor prognosis of PNETS is not generally debated, patients with liver metastasis can benefit from surgical management and other non-operative therapies.[16,17] With a relatively short follow-up, few deaths were observed after recurrence in our study. There was no difference in overall survival between patients with and without recurrence (83% vs 97%, $P=.18$). One study evaluating the recurrence of PNETs showed the same results that patients with recurrence have good long-term overall survival.[7] This may be due to the indolent course of the disease process.

The 2010 and 2017 WHO tumor grade classification differentiate grade 1 from 2 PNETs with a cutoff of Ki67 index <3%. Several studies have demonstrated the significance of WHO grading system in predicting long-term survival for PNETs.[3,18,19] In our study, Ki67 index ≥5% instead of grade 2 was identified to be independently associated with recurrence. Recently, one large scale study with 280 well-differentiated NF-PNETS described the use of the Ki67 index to estimate postoperative recurrence. Same with us, their results showed that only when the cutoff value was increased to Ki67 index ≥5%, the difference of high and low risk for recurrence after surgery was presented.[15] Additionally, several studies showed that the Ki67 cutoff of 5% instead of 3% was effective in predicting disease progression.[11,20,21] However, Harimoto et al[22] showed that WHO tumor grading system was a significant predictor for recurrence in NF-PNETs. In view of the present controversy, our report could provide some insights regarding this issue.

In some cases, lymph node status show no significant predictive value for survival of PNETS.[23,24] Wong et al[25] have reported that lymph node metastasis does not affect overall and disease-free survival. However, related reports identified positive lymph nodes as an independent risk factor for recurrence of PNETS.[7,8,26] For well-differentiated PNETs, lymph node metastasis was significantly associated with malignant potential, such as larger tumor size, higher Ki67 index, higher tumor grade, and neural invasion.[22] In the present study, positive lymph nodes were most strongly associated with recurrence and patients with positive lymph nodes developed recurrence at 7 times the rate of those with negative lymph nodes.

It is still controversial whether tumor size, vascular invasion can be predictors of PNETs. Published reports have demonstrated that tumor size was a significant predictor of recurrence,[27,28] in addition, the European Neuroendocrine Tumor Society (ENETS) suggests that vascular invasion is one of the criteria for assessing the prognosis of PNETs.[2] According to our data, tumor size and vascular invasion were not associated with recurrence. Furthermore, our data showed that almost all of recurrences (11/12, 92%) had an R0 resection and resection margins was not associated with recurrence. In most cases, the resection margin is not significant in predicting recurrence of PNETs.[7,8,15] However, a large, multi-institutional research has demonstrated that R1 margins were associated with tumor recurrence.[29] More high-quality data are needed to demonstrate the relationship between resection margin and recurrence.

As a retrospective analysis, there were several limitations in our study. First, data from the medical records were not complete. For example, perineural invasion, as a significant factor for prognosis of PNETs reported by several studies before, was not available in the pathological reports. Second, the sample was relatively small due to the rarity of the disease which prevented us from making strong conclusions. More multicenter prospective studies are necessary to better understand the recurrence of well-differentiated NF-PNETs.

5. Conclusions

Ki67 index and lymph node status are independently associated with recurrence after resection of well-differentiated NF-PNETs in this study. Patients with high risk of recurrence may need a more frequent follow-up or an adjuvant therapy after surgical resection.

Author contributions

Resources: Neng-wen Ke, Xing Wang.
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Supervision: Xu-Bao Liu, Neng-wen Ke.
Writing – original draft: Qing-quan Tan, Xing Wang.
Writing – review & editing: Le Yang, Yong-Hua Chen, Chun-lu Tan.

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