Original Article

Risk of malignancy and prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors

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Background: Small nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) ≤2 cm have variable biological features, and there is no gold standard treatment for their management. The present study aimed to evaluate the risk of malignancy of small NF-PNETs and their outcomes following curative resection.

Methods: Patients with NF-PNETs undergoing surgical resection at the First Affiliated Hospital, College of Medicine, Zhejiang University, between 2012 and 2017 were included. Clinicopathological characteristics, perioperative results, and prognosis were retrospectively analyzed.

Results: A total of 73 patients were identified, including 28 with small NF-PNETs and 45 large PNETs; 32.1% of NF-PNETs ≤2 cm underwent a parenchyma-sparing pancreas surgery, which was >6.7% in large NF-PNETs. No statistically significant differences in perioperative results, postoperative complications, and long-term outcomes were found between small tumors undergoing standard and parenchyma-sparing pancreatectomy. Eighteen small tumors (64.3%) developed a perioperative complication, with a clinically significant pancreatic fistula rate of 25%; however, only 2 patient needed reintervention. Small NF-PNETs in 3 patients were malignant. Multivariate logistic regression showed that grade ≥3 and lymphovascular invasion were independently related to malignancy in NF-PNETs.

Conclusions: Small NF-PNETs (≤2 cm) are not immune from potential malignancy. Surgical resection may be considered for small tumors and can provide favorable postoperative and long-term outcomes. Parenchyma-sparing pancreatectomy may be an alternative surgery for selected small local NF-PNETs.

Keywords: Nonfunctional pancreatic neuroendocrine tumors (NF-PNETs); malignancy; observation; parenchyma-sparing pancreatectomy

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are a group of endocrine tumors originating from the islet cells of the pancreas and wide heterogeneity, including variable biologic behavior and clinicopathological features (1,2). PNETs are very rare and account for less than 5% of all pancreatic tumors (3-5). However, it has been reported that there has been a significant increase in their incidence over the past several decades, particularly for early/localized PNETs, which is mainly due to the early utility of various advanced imaging tools (6-8). Depending on the presence of clinical syndromes caused by hormone hypersecretion, PNETs are generally divided into the functional type and non-functional type (2). Most PNETs are non-functional

tumors, which comprise about 65–90% of all PNETs and are more aggressive than functional tumors (3,5,7).

Unlike functional PNETs that present with hypersecretion with almost all requiring surgical resection (1), nonfunctional PNETs (NF-PNETs) usually have no apparent symptoms or have non-specific symptoms; there is no gold standard treatment for their management. It is now generally recognized that NF-PNETs >2 cm is the main indication for surgical resection (9,10). However, whether surgery could provide more benefits than non-surgical treatment for NF-PNETs ≤2 cm remains a controversial issue. Recommendations for the treatment of small NF-PNETs were different across guidelines (1,11,12). There are currently two contrasting views regarding the risk of malignancy of NF-PNETs ≤2 cm. These are as follows: (I) small NF-PNETs are usually biologically indolent with rare, aggressive features, and long-term surveillance should be adapted as the primary option (13-15); and (II) a non-negligible risk of malignancy can be observed even in small NF-PNETs; therefore, aggressive surgical treatment is necessary to improve the prognosis (16-18). The primary aim of our study was to evaluate the risk of malignancy of small NF-PNETs ≤2 cm, and to explore further the effect of surgical resection based on our single-center experience. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-582).

Methods

Date collection

Medical records, radiologic reports, and pathologic results of all patients with PNETs at the First Affiliated Hospital of Zhejiang University between January 2012 and December 2017 were reviewed retrospectively. Patients who underwent curative resection and had pathologically confirmed NF-PNETs were included in our study. The exclusion criteria were as follows: (I) patients with incomplete medical data; (II) patients diagnosed with inherited diseases, including, but not limited to, multiple neuroendocrine neoplasia types 1 (MEN1) and Von Hippel-Lindau; (III) patients with a functional PNET neoplasm; (IV) patients who had undergone an R2 resection; and (V) recurrence of a preoperatively resected PNET. Eligible patients were divided into two groups according to their tumor sizes, the small tumor group (≤2 cm) and the large tumor group (>2 cm). All pathological reports were reviewed carefully and available slides were revised by an experienced pathologist. Tumor size was determined by the maximum diameter of the tumor in the pathological report. All tumors were classified according to the World Health Organization 2017 Grading of Recommendations Assessment, Development and Evaluation criteria, and the European Neuroendocrine Tumor Society (ENETS) classification system. Malignant signs of NF-PNETs were defined as the presence of tumor recurrence or nodal/distant metastases (synchronous or metachronous). The study was conducted in accordance with the Declaration of Helsinki as revised in 2013. This study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. IIT20200277A) and all patient information was anonymous. Individual consent for this retrospective analysis was waived.

Surgery procedures and complications

Curative surgery was defined as R0 (absence of residual tumor under a microscope) or R1 (presence of residual tumor under a microscope) resection. For patients with resectable metastasis or invasive disease at the time of diagnosis, curative intent surgery contained simultaneous resection of the primary tumor and all metastases or invasion lesions. The surgical procedure included standard surgery such as pancreaticoduodenectomy (Whipple), distal pancreatectomy with or without splenectomy, total pancreatectomy and parenchyma-sparing pancreatectomy, which contained enucleation and central pancreatectomy. Clavien-Dindo classification was used to stratify postoperative comorbidities. Perioperative mortality was defined as in-hospital or within 60-day death. Long-term complications contain new-onset diabetes mellitus or worsen of diabetes mellitus, and pancreatic exocrine insufficiency.

Follow-up and survival

Follow-up data were obtained from postoperative outpatient visits records or telephone contact. The last follow-up was terminated in January 2020. Patients lost to follow-up were censored at the date of the last contact. Recurrence of NF-PNETs was defined as the presence of a local lesion or nodal/distant metastasis and determined by biopsy pathological findings and imaging. Disease-free survival (DFS) was calculated as the time between surgery and recurrence or metastasis or final follow-up. Overall survival (OS) was defined as the time between surgery and death or

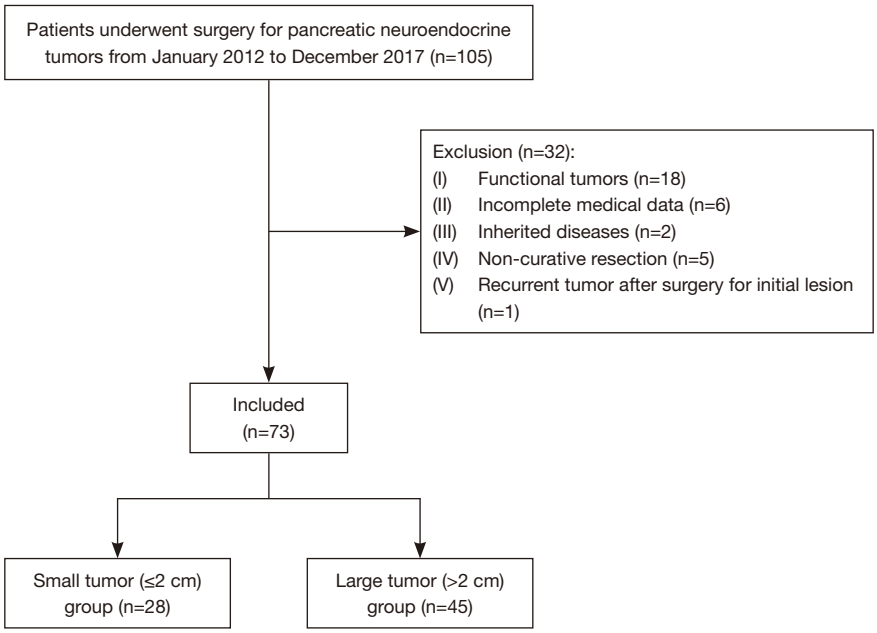

Figure 1 Flow chart of the patient selection process.

the last follow-up. The cause of death was investigated and defined if this was related to NF-PNETs.

Statistical analysis

Continuous variables with normal distribution were expressed as means ± standard deviations; medians and ranges were described used for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. The comparison of characteristics between two independent samples was performed using χ^2-test or Fisher's exact test for categorical data, Student's *t*-test, or the Mann-Whitney U-test for continuous variables. Survival analysis was calculated using the Kaplan-Meier method and compared by the log-rank test. A stepwise binary logistic regression model was used to evaluate significant predictors associated with malignancy. Two-sided P value <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistic version 22.0 (IBM, Chicago, IL, USA).

Results

Clinical and demographic characteristics

A total of 73 patients with NF-PNETs who underwent curative-intent surgery were included in our study (*Figure 1*). Patients' baseline characteristics are presented in *Table 1*. Twenty-eight small tumors had a median size of 1.2 cm, with the minimum dimension being 0.7 cm. Forty-five patients (57.8% women, n=26) were in large tumor group (>2 cm). More than half of the patients (52.1%) did not have symptoms. Tumors located in the body/tail accounted for 65.8% (n=48) of all patients, while only 25 (34.2%) were located in the head/neck. There were no significant differences associated with age, sex, symptoms, and tumor site between the small and large tumors.

Surgical results

Surgery procedures and postoperative complications are shown in *Table 2*. Parenchyma-sparing pancreatectomy was more frequently preferred to treat the small PNETs rather than the large PNETs (32.1% *vs.* 6.7%, P=0.011). The majority of the patients (76.7%, n=56) underwent open surgery, whereas 17 patients (23.3%) underwent laparoscopy. Of the 28 patients with small NF-PNETs, 18 (64.3%) developed a perioperative complication, and 2 (11.1%) required reintervention. The rate of pancreatic fistula grade B/C was 25%. Worsening glucose control and exocrine insufficiency were observed in 5 (17.9%) and 6 (21.4%) cases, respectively. There were no statistically significant differences in perioperative results, postoperative

Table 1 Clinical features and histopathology of patients with nonfunctional pancreatic neuroendocrine tumors

Variables	Total (n=73)	≤2 cm (n=28)	>2 cm (n=45)	P value
Age, years, mean [SD]	56 [11]	59 [10]	55 [10]	0.090
Gender				0.725
Male	32 (43.8)	13 (46.4)	19 (42.2)	
Female	41 (56.2)	15 (53.6)	26 (57.8)	
Symptom				0.838
No	38 (52.1)	15 (53.6)	23 (51.1)	
Yes	35 (47.9)	13 (46.4)	22 (48.9)	
Abdominal pain/discomfort	28 (38.4)	9 (32.1)	19 (42.2)	0.389
Jaundice	4 (5.5)	1 (3.6)	3 (6.7)	0.971
Weight loss	3 (4.1)	1 (3.6)	2 (4.4)	1.000
Fatigue	2 (2.7)	2 (7.1)	0 (0.0)	0.144
Site				0.765
Head/neck	25 (34.2)	9 (32.1)	16 (35.6)	
Body/tail	48 (65.8)	19 (67.9)	29 (64.4)	
Ki-67, median [range]	5 [1–50]	1 [1–30]	7 [1–50]	<0.001
WHO grade				<0.001
G1	27 (37.0)	19 (67.9)	8 (17.8)	
G2	38 (52.1)	6 (21.4)	32 (71.1)	
G3	7 (9.6)	3 (10.7)	4 (8.9)	
NEC	1 (1.4)	0 (0.0)	1 (2.2)	
ENETS staging				0.001
I–II	51 (69.9)	26 (92.9)	25 (55.6)	
III–IV	22 (30.1)	2 (7.1)	20 (44.4)	
Lymph node status				0.680
Positive	7 (9.6)	1 (3.6)	6 (13.3)	
Negative	31 (42.5)	9 (32.1)	22 (48.9)	
Unknown	35 (47.9)	18 (64.3)	17 (37.8)	
Lymphovascular invasion				0.003
Present	22 (30.1)	3 (10.7)	20 (44.4)	
Absent	51 (69.9)	25 (89.3)	25 (55.6)	
Perineural invasion				0.862
Present	6 (8.2)	3 (10.7)	3 (6.7)	
Absent	67 (91.8)	25 (89.3)	42 (93.3)	
Distant metastasis before surgery				0.149
Yes	5 (6.8)	0 (0.0)	5 (88.9)	
No	68 (93.2)	28 (100.0)	40 (11.1)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=73)	≤2 cm (n=28)	>2 cm (n=45)	P value
Adjuvant therapy				1.000
Yes	6 (8.2)	2 (7.1)	4 (8.9)	
No	67 (91.8)	26 (92.9)	41 (91.9)	
Recurrence				0.053
Yes	15 (20.5)	2 (7.1)	13 (28.9)	
No	58 (79.5)	26 (92.9)	32 (71.1)	
Malignancy				0.057
Yes	18 (24.7)	3 (10.7)	15 (33.3)	
No	55 (75.3)	25 (89.3)	30 (66.7)	
Follow-up, months, mean (SD)	49.6 (24.5)	52.5 (22.8)	47.8 (25.5)	0.428
Death	4 (5.5)	0 (0.0)	4 (8.9)	0.291

Numbers in brackets represent percentage frequency if not otherwise specified. SD, standard deviation.

complications, and long-term outcomes between small tumors with and without parenchyma-sparing pancreatectomy (*Table 3*).

Pathological results

Postoperative pathological results are summarized in *Table 1*. Small tumors were more likely to have a better differentiation grade than large tumors, with 67.9% being G1 (n=19), compared to 17.8% (n=8) of large NF-PNETs. However, the rate of grade ≥3 [NET-G3 and neuroendocrine carcinoma (NEC)] was 10.7% in small tumors, which was similar to the large tumors (11.1%). The Ki-67 index was apparently lower in small NF-PNETs than in large NF-PNETs (P<0.001). Large tumors (>2 cm) had a greater proportion of ENETS stage III–IV, which tended to show frequent infiltrating or metastatic diseases, whereas small tumors tended to be local with early staging (ENETS staging I–II, 92.9% *vs.* 55.6%, P=0.001). One tumor with a diameter of 1.5 cm was found to have positive lymph nodes after a careful pathological examination. A statistically significant difference in lymphovascular invasion were noted between the 2 groups; the lymphovascular invasion was more frequent in NF-PNETs >2 cm (P=0.003).

Long-term outcomes

After a mean follow-up period of 49.6±24.5 months (range, 1–94 months), 6 cases were lost to follow-up. A total of 15 patients had tumor recurrence or metastasis after curative-intent surgery with a median time to recurrence of 13 months; 2 were small NF-PNETs, and the remaining 13 were large tumors (*Table 1*). The liver was the most common recurrence site of recurrence (n=11), followed by lymph nodes (n=2). In total, four patients developed disease-related deaths, all of them were large tumors. There were no deaths due to other causes.

The difference in OS between the small and large tumor groups was not significant (P=0.105) (*Figure 2A*), while small NF-PNETs had better significantly better DFS than large NF-PNETs (P=0.023) (*Figure 2B*). For the 35 patients with symptoms, DFS did not differ from those who were asymptomatic (P=0.412) (*Figure 2C*). There were statistically significant differences in DFS in patients with tumors of different pathological grades (P<0.001) (*Figure 2D*).

Risk of malignancy of the NF-PNETs

A total of three patients with small NF-PNETs (10.7%) had symptoms of malignancy; 2 had a postoperative recurrence, and 1 had synchronous lymph node metastasis at the time of diagnosis. Baseline characteristics of 18 patients with NF-PNETs showing malignant signs are shown in *Table 4*. Variables associated with the presence of malignancy were assessed by univariate and multivariate logistic regression analysis (*Table 5*). Univariate analysis indicated that sex,

Table 2 Surgical procedures and complications of nonfunctional pancreatic neuroendocrine tumors that underwent curative resection

Variable	Total (n=73)	≤2 cm (n=28)	>2 cm (n=45)	P value
Surgery procedure				0.021
Whipple	18 (24.7)	4 (14.3)	14 (31.1)	
DP	17 (23.3)	9 (32.1)	8 (17.8)	
DP+ splenectomy	25 (34.2)	6 (21.4)	19 (42.2)	
Central resection	5 (6.8)	4 (14.3)	1 (2.2)	
Enucleation	7 (9.6)	5 (17.9)	2 (4.4)	
TP+ splenectomy	1 (1.4)	0 (0.0)	1 (2.2)	
Surgery type				0.011
Standard surgery	61 (83.6)	19 (67.9)	42 (93.3)	
Parenchyma-sparing pancreatectomy	12 (16.4)	9 (32.1)	3 (6.7)	
Approach				
Open surgery	56 (76.7)	19 (67.9)	37 (82.2)	0.158
Laparoscopic surgery	17 (23.3)	9 (32.1)	8 (17.8)	
Operative time, min, mean [SD]	322 [143]	342 [145]	309 [143]	0.336
Blood loss, mL, median [range]	200 [25–2,000]	200 [25–300]	200 [50–2,000]	0.108
Surgical margin				
R0	71 (97.3)	27 (96.4)	44 (97.8)	1.000
R1	2 (2.7)	1 (3.6)	1 (2.2)	
Length of stay, days, median [range]	16 [5, 71]	13 [6, 71]	14 [5, 44]	0.682
Complications				0.357
No	31 (42.5)	10 (35.7)	21 (46.7)	
Yes	42 (57.5)	18 (64.3)	24 (53.3)	
Severity				0.661
Clavien-Dindo ≤II	65 (81.0)	26 (92.9)	39 (86.7)	
Clavien-Dindo ≥III	8 (19.0)	2 (7.1)	6 (13.3)	
POPF	28 (38.4)	14 (50.0)	14 (31.1)	0.107
POPF grade B/C	11 (15.1)	7 (25.0)	4 (8.9)	0.125
DGE	4 (5.5)	1 (3.6)	3 (6.7)	0.971
Abdominal collection	8 (10.9)	3 (10.7)	5 (11.1)	1.000
Abdominal bleeding	1 (1.4)	0 (0.0)	1 (2.2)	1.000
Biliary leakage	1 (1.4)	0 (0.0)	1 (2.2)	1.000
Chylous leakage	2 (2.7)	2 (7.1)	0 (0.0)	0.144
Endocrine insufficiency	12 (16.4)	5 (17.9)	7 (15.6)	0.796
Exocrine insufficiency	17 (23.3)	6 (21.4)	11 (24.4)	0.767

Numbers in brackets represent percentage frequency if not otherwise specified. DP, distal pancreatectomy; TP, total pancreatectomy; SD, standard deviation; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying.

Table 3 Comparison of parenchyma-preserving pancreatectomy and standard surgery for small nonfunctional pancreatic neuroendocrine tumors

Factors	Parenchyma-preserving pancreatectomy (n=9)	Standard surgery (n=19)	P value
Operation time, min, mean (SD)	288.3 (169.4)	368.0 (128.6)	0.179
Surgery approach			0.195
Open	8 (88.9)	11 (57.9)	
Minimal invasive	1 (11.1)	8 (42.1)	
Blood loss, mL, median (range)	147.2 (25.0–250.0)	186.6 (50.0–300.0)	0.315
Length of stay, days, median [range]	17 [6–71]	20 [6–71]	0.844
Surgical margin			0.321
R0	8 (88.9)	19 (100.0)	
R1	1 (11.1)	0 (0.0)	
Complications, n (%)			0.677
No	4 (44.4)	6 (31.6)	
Yes	5 (55.6)	13 (68.4)	
Severity (Clavien-Dindo grade)			1.000
CD ≤2	9 (100.0)	17 (89.5)	
CD ≥3	0 (0.0)	2 (10.5)	
POPF	5 (55.6)	9 (47.4)	1.000
POPF grade B/C	5 (55.6)	4 (21.1)	0.097
Endocrine insufficiency	0 (0.0)	5 (26.3)	0.144
Exocrine insufficiency	2 (22.2)	4 (21.1)	1.000
Recurrence	0 (0.0)	2 (10.5)	1.000
Disease-related death	0 (0.0)	0 (0.0)	1.000

Numbers in brackets represent percentage frequency if not otherwise specified. SD, standard deviation; POPF, postoperative pancreatic fistula.

tumor grade, lymphovascular invasion, perineural invasion and tumor size were significantly related to malignancy in NF-PNETs that underwent curative resection. These factors were included in a stepwise multivariate logistic regression model, whereas the presence of malignancy signs was only found to be associated with tumor grade and lymphovascular invasion.

Discussion

The definition of malignancy in NF-PNETs varied among different studies. Boninsegna *et al.* defined malignant NF-PNETs as tumors that had extra-pancreatic invasion or metastasis (19), whereas Regenet *et al.* define these as the presence of synchronous or metachronous metastases, including nodal and hepatic metastases (20). In addition to metastasis, histopathological grade ≥2 or 3 was also added to this definition (14,21). Given that a considerable proportion of patients with tumors ≥G2 had no recurrence or metastasis, tumor grade is probably just a clinicopathological predictor of malignancy. For this reason, malignancy in NF-PNETs was defined as the existence of tumor recurrence or nodal/distant metastasis (synchronous or metachronous) in the present study.

Primary tumor size is associated with clinical T-stages criteria according to the ENETS/American Joint Committee on Cancer (AJCC) TNM classification staging system. Significant differences in outcome comparing

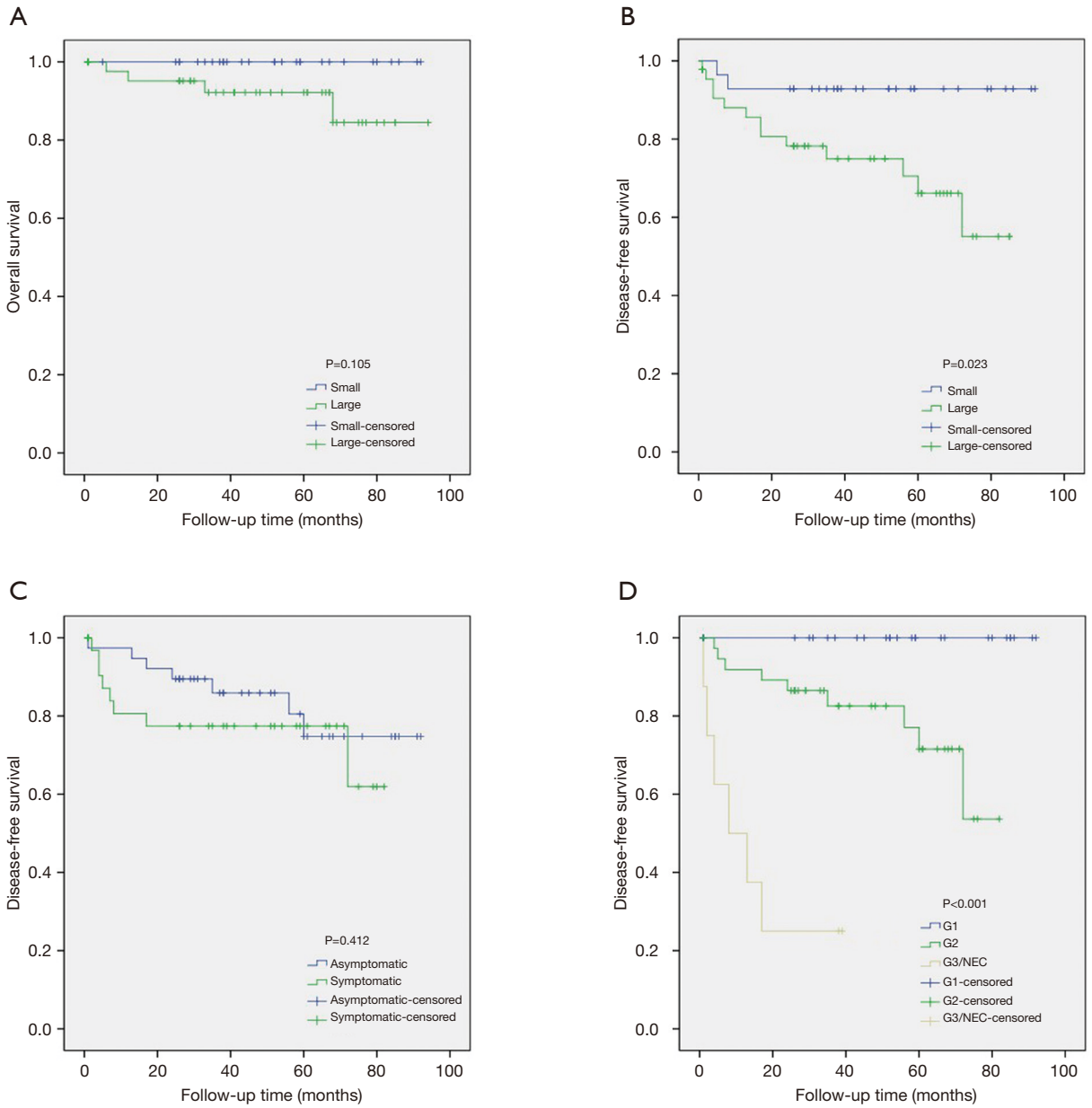

Figure 2 Kaplan-Meier curves of overall survival (OS) and disease-free survival (DFS) in patients with nonfunctional pancreatic neuroendocrine tumors. Patients with small tumors had similar OS (A), but better DFS than those with large tumors (B). DFS did not differ between patients with symptoms and those without (C). There were statistically significant differences in DFS in patients with tumors of different pathological grades (D).

T-stage has been shown in many previously published papers and 2 cm has been widely adopted as the cutoff point in determining the biologic features of NF-PNETs (22). For small (≤2 cm) NF-PNET, there remains controversy over their biological behaviors. Kurita *et al.* performed a retrospective analysis of 23 patients with small sporadic NF-PNETs who were observed and found no tumor progression or nodal/distant metastases (23). A systematic review conducted by Sallinen *et al.* revealed that only 22% of 344 patients with sporadic small PNETs developed tumor growth and no patient developed nodal or distant metastasis (24). However, some reports have indicated

Table 4 Baseline characteristics of 18 patients with symptoms of malignancy of nonfunctional pancreatic neuroendocrine tumors

Variable	Total (n=18)	≤2 cm (n=3)	>2 cm (n=15)
Age, years, mean [SD]	58 [8]	62 [9]	57 [8]
Gender			
Male	12 (66.7)	3 (100.0)	9 (60.0)
Female	6 (33.3)	0 (0.0)	6 (40.0)
Symptom			
Yes	10 (55.6)	2 (66.7)	8 (53.3)
No	8 (44.4)	1 (33.3)	7 (46.7)
Site			
Head/tail	8 (44.4)	1 (33.3)	7 (46.7)
Body/tail	10 (55.6)	2 (66.7)	8 (53.3)
WHO grade			
G1	0 (0.0)	0 (0.0)	0 (0.0)
G2	11 (61.1)	1 (33.3)	10 (66.7)
G3	6 (33.3)	2 (66.7)	4 (26.7)
NEC	1 (5.6)	0 (0.0)	1 (6.7)
Lymphovascular invasion			
Present	13 (72.2)	2 (66.7)	11 (73.3)
Absent	5 (27.8)	1 (33.3)	4 (26.7)
Perineural invasion			
Present	4 (22.2)	2 (66.7)	2 (13.3)
Absent	14 (77.8)	1 (33.3)	13 (86.7)
Size, cm, mean (SD)	4.4 (2.2)	1.8 (0.3)	4.9 (2.0)
Surgery type			
Standard surgery	17 (94.4)	3 (100.0)	14 (93.3)
Parenchyma-sparing surgery	1 (5.6)	0 (0.0)	1 (6.7)
Surgery approach			
Open	16 (88.9)	2 (66.7)	14(93.3)
Laparoscopically	2 (11.1)	1 (33.3)	1 (6.7)
Surgical margin			
R0	18 (100.0)	3 (100.0)	15 (100.0)
R1	0 (0.0)	0 (0.0)	0 (0.0)
Death	4 (22.2)	0 (0.0)	4 (26.7)
Follow-up, months, mean (SD)	46.6 (28.1)	36.3 (30.1)	48.6 (28.4)

Numbers in brackets represent percentage frequency if not otherwise specified. SD, standard deviation.

Table 5 Univariate and multivariate logistic regression analyses of the risk factors associated with malignancy in patients with nonfunctional pancreatic neuroendocrine tumors

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	1.020 (0.968–1.074)	0.462	–	–
≤60	Reference	–	–	–
> 60	1.644 (0.555–4.876)	0.370	–	–
Sex				
Male	Reference	–	–	–
Female	0.286 (0.093–0.879)	0.029	–	–
Symptom				
No	Reference	–	–	–
Yes	1.615 (0.553–4.715)	0.381	–	–
Tumor site				
Head/neck	Reference	–	–	–
Body/tail	0.559 (0.188–1.666)	0.297	–	–
Grade				
G1/2	Reference	–	Reference	–
≥G3	34.364 (3.833–308.064)	0.002	39.160 (3.360–456.417)	0.003
Lymphovascular invasion				
Absent	Reference	–	Reference	–
Present	11.700 (3.392–40.361)	<0.001	12.815 (2.962–55.449)	0.001
Perineural invasion				
Absent	Reference	–	–	–
Present	7.571 (1.256–45.651)	0.027	–	–
Surgery type				
Standard surgery	Reference	–	–	–
Parenchyma-sparing surgery	0.235 (0.028–1.965)	0.181	–	–
Surgery approach				
Open	Reference	–	–	–
Laparoscopic	0.333 (0.068–1.627)	0.174	–	–
Size, cm				
≤2	Reference	–	–	–
>2	4.167 (1.082–16.048)	0.038	–	–

OR, odds ratio; CI, confidence interval.

that small tumors can recur or metastasize, and as tumor size was not significantly associated with the prognosis of NF-PNETs (17,25,26). Consistent with the previous reports, 3 of 28 small tumors in our study recurred and metastasized. Despite an obvious difference in DFS between small tumors and large tumors (P=0.023), there were no statistically significant differences in the rates of malignancy (P=0.057). Further, tumor size was not significantly correlated with the risk of malignancy in the multivariate analysis. The smallest tumor size with malignancy was 1.5 cm in our study, similar to those reported previously (18,27). Alternative tumor size cutoff points have been shown to effectively discriminate between benign and malignant NF-PNETs (20,23,28). However, some previously published studies have indicated that even very small PNETs (<0.5 cm) could pose a significant risk of nodal or distant metastasis (8,26), indicating that NF-PNETs of all sizes should be considered potentially malignant.

Controversy exists regarding the choice between active resection and conservative observation for patients with small NF-PNETs. ENETS guidelines recommend surgical resection for patients with small NF-PNETs, and observation for young patients who have small NF-PNETs <2 cm affected by MEN1 syndrome or those who have a severe comorbidity and are ineligible for surgery (11). However, the National Comprehensive Cancer Network and the North American Neuroendocrine Tumor Society suggest observation for smaller than 1 cm in size, low-grade, incidentally discovered NF-PNETs (1,12). Recently, published studies with large sample size have indicated that the resection of PNETs ≤2 cm is associated with better survival than observation, and surgery result in significantly better survival in patients with PNETs 1–2 cm but not those with PNETs <1 cm (29,30). From a radical cure perspective, surgical resection should be considered first, if tumors can be completely resected. Nevertheless, surgeons must carefully consider the potential benefits and complications of surgery before the procedure.

In our series, although the overall perioperative comorbidity of small NF-PNETs was high at 64.3%, only a small proportion of them had serious complications (11.1%); however, there were no mortalities. The rate of clinically relevant postoperative pancreatic fistulas was 25%, which was in agreement with the rates reported by other authors (28,31). However, although postoperative complications were common, perioperative mortality rates were very low for surgical resection of small PNETs, ranging from 0% to 3.6% in the literature (31,32), which compares favorably with the reported 6–10% rates of in-hospital mortality after pancreatectomy at the national level (28). Also, regarding long-term pancreatic function, the rates of postoperative endocrine and exocrine pancreatic insufficiency in the present study were similar to those reported by others (23,33). According to previously published studies, the recurrence rate of small NF-PNETs that underwent curative resection ranged from 5.4% to 11% (18,20,28), consistent with our study (7.1%). Taken together, patients with small NF-PNETs can be considered for surgical management, which is considered the only possible cure for NF-PNETs; surgical resection can provide a very high cure rate for small NF-PNETs, with good postoperative and long-term outcomes. And prospective randomized clinical trials are need to confirm whether surgical resection can provide survival benefit for small NF-PNETs of different tumor size groups.

In the present study, the small tumor group had a higher rate of clinically important pancreatic fistula than the large tumor group, but the difference was not significant (P=0.125). One plausible explanation for this is that patients with small NF-PNETs were likely to undergo parenchyma-sparing resection than those with large NF-PNETs (32.1% *vs.* 6.7%, P=0.011). It has been shown that parenchyma-sparing surgery has a higher rate of pancreatic fistula than standard pancreatic resection (1,34), which could be because enucleation provides a close resection margin to the main pancreatic duct, and central pancreatectomy has two pancreatic stumps (10). Parenchyma-sparing procedures tend to have a shorter operative time, lesser blood loss but higher postoperative morbidity compared to standard pancreatic resection (4,10). However, the increased risk of postoperative morbidity, particularly pancreatic fistula, was not found to be associated with a higher in-hospital mortality rate (34,35). As *Table 3* shown, parenchyma-sparing resection for small NF-PNETs provided comparable operative results, complications and long-term outcomes than standard surgery, which is in line with previous studies (31,35). Notably, among 18 patients with malignant NF-PNETs, only one patient who developed late liver metastasis underwent parenchyma-sparing resection. However, neither tumor size nor surgery type indicated a close association with malignancy in the multivariate analysis. This difference could be because large tumors comprised most of the study sample (n=45, 61.6%), and had more frequent lymphovascular invasion than small NF-PNETs (P=0.003), making it more common to perform a standard pancreatic resection. According to

these results, parenchyma-sparing resection could be used as an alternative for small local NF-PNETs in the absence of adjacent infiltration or metastasis. In contrast, for those large, regional invasion or metastasis, standard surgery should be the primary procedure.

The present study had several limitations. First, the study was inherently limited by its retrospective nature, which did not include patients that accepted non-operative management, and we could not assess the natural history of small NF-PNETs and determine the benefits of surgery. Second, the relatively small sample size from a single center may have affected the results and limited further subgroup analyses on small NF-PNETs of different tumor sizes. Third, the overall median follow-up period was relatively short (49.6±24.5 months); together with relatively higher disease-specific survival, it was difficult to determine the prognostic factors affecting OS. To better assess the risk of malignancy of small NF-PNETs and to evaluate the impact of surgical intervention on small NF-PNETs of different tumor size groups, multicenter studies with large sample size, and prospective randomized trials are needed.

Despite its limitations, the current study showed that small NF-PNETs are not immune from potential malignancy compared to NF-PNETs >2 cm, and surgical resection may be considered and can present favorable postoperative and long-term outcomes for small tumors. Parenchyma-sparing pancreatectomy may be an alternative for selected small local NF-PNETs. Further research is needed to confirm whether surgery is beneficial for small NF-PNETs of different tumor size groups than nonsurgical management.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki as revised in 2013. This study was approved by Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (NO.: IIT20200277A) and individual consent for this retrospective analysis was waived.

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