Ann Surg Oncol (2017) 24:1127–1133
DOI 10.1245/s10434-016-5663-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Pancreatic Duct Involvement in Well-Differentiated Neuroendocrine Tumors is an Independent Poor Prognostic Factor

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ABSTRACT

Background. The biological behavior of well-differentiated neuroendocrine tumors of the pancreas (PNETs) is difficult to predict. This study was designed to determine whether involvement of the main pancreatic duct (MPD) serves as a poor prognostic factor for PNETs.

Methods. The involvement of the MPD in PNETs was defined as ductal stenosis inside the tumor mass associated with distal MPDs more than twofold larger in diameter than the proximal ducts. We examined the correlation between MPD involvement and other clinicopathological parameters, including nodal metastasis and recurrence-free survival, in 101 patients treated consecutively at three referral centers in Japan. All patients underwent surgical resection.

Results. MPD involvement was observed in 13 of the 101 cases (13%) and was associated with multiple unfavorable clinicopathological features (e.g., larger tumor size, higher histological grade, more frequent nodal metastasis, and higher recurrence rates). Patients with MPD involvement also showed significantly worse recurrence-free survival than did those without ductal involvement ($P < 0.001$), with a 5 years recurrence-free rate of 41%. On multivariate analysis, MPD involvement was significantly associated with nodal metastasis [odds ratio (OR) 16; 95% confidence interval (CI) 3.8–89; $P < 0.001$] and recurrence (OR 8.0; 95% CI 1.7–46; $P = 0.009$). The radiology–pathology correlation revealed that stenosis of the MPD was due to periductal and/or intraductal tumor invasion. Cases with MPD involvement had microscopic venous invasion ($P = 0.010$) and perineural infiltration ($P = 0.002$) more frequently than did those with no ductal infiltration.

Conclusions. MPD involvement in PNETs may serve as an imaging sign indicating an aggressive clinical course.

Well-differentiated pancreatic neuroendocrine tumors (PNETs) are a rare form of epithelial neoplasm that has been increasingly diagnosed worldwide over the past several decades.[1,2] Complete resection is the cornerstone of clinical management and the sole curative option for patients with PNETs.[3] The clinical courses of PNETs are diverse and difficult to predict.[4–8] The most widely accepted prognostic factor is the World Health Organization (WHO) histological grading scheme, in which PNETs are classified into G1, G2, and G3 based on mitotic counts and Ki-67 labeling indices.[9,10] However, because this classification system requires tissue specimens, a preoperative assessment for the risk of malignancy is generally difficult in patients with PNET.[11]

Previous studies have shown that tumor size is one of the most reliable, noninvasive predictors for nodal and distant metastases.[1,2,4,12] However, a larger tumor size

First Received: 26 August 2016;
Published Online: 7 November 2016

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alone is far less reliable to determine aggressive clinical behavior in clinical practice.[3,13] Therefore, new preoperative factors that can be assessed in the clinical setting have been needed. We recently observed that some patients with PNETs who presented with stricture of the main pancreatic duct (MPD) showed a malignant clinical course. A review of the literature found similar case reports, which prompted us to speculate that MPD involvement in PNETs may indicate a poor prognosis.[14–17]

Based on our hypothesis, this multicenter, retrospective study was conducted to examine the clinical significance of MPD involvement in PNETs in a systematic way.

METHODS

Case Selection

The study protocol was approved by the Ethics Committee at Kobe University Graduate School of Medicine. Between January 2004 and April 2016, 110 patients with well-differentiated PNETs were surgically treated at our institutes [Kobe University Hospital ($n = 55$), Kindai University Hospital ($n = 30$), and Kagawa University Hospital ($n = 25$)]. Eight incidental PNETs found in surgical specimens resected for other purposes were excluded. Another patient who had both PNET and intraductal papillary mucinous neoplasm (IPMN) also was excluded from this study, because it was difficult to determine whether the duct dilatation was due to PNET or IPMN.

Study Cohort

The study cohort consisted of 49 men and 52 women with a median age of 64 (range 23–87) years at the time of resection. Twenty-five cases (25%) were functioning (21 insulinomas, 3 gastrinomas, and 1 VIPoma). Three patients had multiple endocrine neoplasia type 1, whereas two others had a history of von Hippel–Lindau disease. Standard surgical procedures with regional lymph node dissection were performed in the following 66 of 101 cases (65%): pancreatoduodenectomy ($n = 28$), distal pancreatectomy ($n = 37$), and total pancreatectomy ($n = 1$). Organ/parenchymal-sparing resections [spleen-preserving distal pancreatectomy ($n = 10$), central pancreatectomy ($n = 7$), or enucleation ($n = 18$)] were considered for small tumors (<20 mm) without any signs of metastasis. Complete resection was achieved in 98 of 101 patients (97%). Seven patients with G1 PNETs (5–12 mm at the greatest diameter) were followed at an outpatient clinic and subjected to repeat contrast-enhanced computed tomography (CT) every 12 months. The remaining patients followed were subjected to repeat CT every 3–6 months during the first 2–3 years and yearly thereafter. Additional magnetic resonance imaging, endoscopic ultrasonography, and positron emission tomography studies were performed if recurrence was suspected. The median follow-up time was 43 (range 2–133) months.

Data Collection

Medical records, imaging data, and histology slides were reviewed retrospectively in terms of age, sex, tumor size, number of tumors, tumor location, and tumor functionality. Tumor sizes were measured based on the last enhanced CT scans before to surgery. For patients with multiple PNETs, the largest tumor was evaluated. Tumors were graded based on Ki-67 indices and mitotic counts, according to the WHO classification.[18]

Definition of MPD Involvement

The presence or absence of MPD involvement was evaluated retrospectively on magnetic resonance cholangiopancreatography (MRCP) images by at least two experienced pancreatic surgeons at each institution. In the preliminary study performed in the Kobe University cohort ($n = 51$), the accuracy of MRCP and that of enhanced CT for diagnosing MPD involvement were in 100% agreement. Therefore, enhanced CT data were used alternatively for cases with no available MRCP data (36/101 cases, 36%). MPD involvement was defined as stenosis of the MPD in the tumor mass associated with up-stream dilatation of the MPD more than double the diameter of the proximal part of the MPD. MPD dilatation from other causes was excluded.

Immunohistochemical Study

In the Kobe University cohort ($n = 51$), original hematoxylin and eosin-stained sections were further reviewed for histological changes representing MPD stenosis. Microscopic venous and lymphatic invasion and perineural infiltration were evaluated using immunostaining for CD31 and D2-40 as described previously.[19] Preoperative serum pancreatic amylase and lipase levels also were measured to determine parenchymal injury due to ductal obstruction.

Statistics

To identify predictors of a progressive clinical course of PNET, clinicopathological factors were correlated with nodal metastases or recurrence. Tumor recurrence was evaluated instead of overall survival, as PNETs are slow-

growing neoplasms requiring longer follow-up periods for analyzing patient survival. Analyses were performed with the Fisher's exact test for categorical variables and the Wilcoxon test for a continuous variable. A two-sided P value <0.05 was considered statistically significant. Univariate analyses were performed with logistic regression models, and variables with P values <0.05 were further evaluated in a multivariate logistic regression model to calculate an adjusted odds ratio (OR) with 95% confidence intervals (CI). Survival curves were estimated with the Kaplan–Meier method and compared by the log-rank test. All analyses were performed with JMP 11.0 for Macintosh (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

MPD involvement was observed in 13 of 101 patients (13%). Figure 1a shows a representative MRCP image of stenosis and upstream dilatation of the MPD. Table 1 compares multiple clinicopathological parameters between patients with and without ductal involvement. PNETs with MPD involvement were all nonfunctioning and were significantly larger in size and more common in the pancreatic head than those without ductal involvement. The most significant difference was noted in the rate of nodal metastasis [10/13 (77%) with involvement vs. 11/88 (13%) without involvement; $P < 0.001$]. During follow-up, 6 of 12 PNET cases (50%) with MPD involvement and 6 of 86 PNET cases (7%) without MPD involvement had recurrence ($P < 0.001$). Recurrent tumors developed in the liver ($n = 9$) or multiple organs ($n = 3$).

Evaluation of the Clinical Impact of Stenotic Involvement of the MPD

The Kaplan–Meier curve (Fig. 2) illustrated that patients with PNETs with MPD involvement had a shorter recurrence-free period than did those without MPD involvement. The 5 years recurrence-free rate of patients with PNETs with MPD involvement was 41%, which was lower than that of patients with PNETs ≥ 15 mm (75%) or G2 PNETs (74%).

Multivariate analysis also was conducted to determine whether MPD involvement is an independent prognostic factor. Seven potential prognostic features (age, sex, tumor size, tumor location, functionality, MPD involvement, and histological grade) of nodal metastasis and tumor recurrence were evaluated by univariate analysis (Table 2). Those factors significantly associated with nodal metastasis on univariate analysis, tumor size ($P < 0.001$), MPD involvement ($P < 0.001$), and histological grade ($P = 0.002$) were subjected to multivariate analysis, which revealed MPD involvement ($P < 0.001$) as an independent factor significantly correlated with nodal metastasis. For tumor recurrence, tumor size ($P < 0.001$), MPD involvement ($P < 0.001$), and histological grade ($P < 0.001$) were

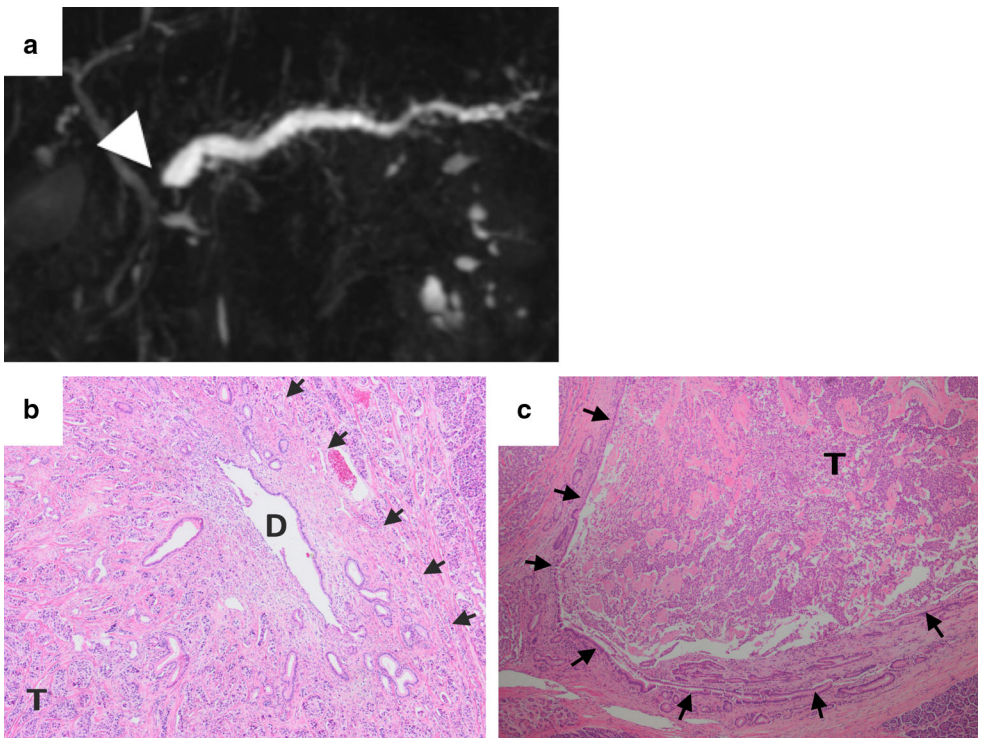

FIG. 1 Representative radiological and histopathological findings for MPD involvement in PNETs. **a** Representative magnetic resonance cholangiopancreatography showing stenosis (*arrowhead*) and upstream dilatation of the MPD. **b** The MPD (D) entrapped in the tumor (T) appears to be narrow due to periductal tumor infiltration (original magnification 40×). Unlike classic PNETs, the tumor is associated with fibrotic stroma. *Arrows* indicate the border between the tumor and the background parenchyma. **c** The tumor (T) shows extensive intraductal infiltration (original magnification 40×). *Arrows* indicate the MPD. *MPD* main pancreatic duct, *PNET* pancreatic neuroendocrine tumor

TABLE 1 Patient characteristics

Variable	Patients	MPD involvement		*P* value
	$n = 101$	Negative	Positive	
Age (*n*)				
<65 years	52	43	9	0.237
≥65 years	49	45	4	
Sex (*n*)				
Female	52	46	6	0.771
Male	49	42	7	
Tumor size (*n*)				
<15 mm	43	42	1	0.006*
≥15 mm	58	46	12	
No. of pancreatic masses (*n*)				
Single	96	83	13	1.000
Multiple	5	5	0	
Tumor location (*n*)				
Head	37	28	9	0.013*
Body–tail	64	60	4	
Type of hormone production (*n*)				
Non-functioning	76	63	13	0.034*
Functioning	25	25	0	
Nodal metastasis (*n*)				
Negative	80	77	3	<0.001*
Positive	21	11	10	
Distant metastasis (*n*)				
Negative	95	85	10	0.027*
Positive	6	3	3	
Histological classification (*n*)				
G1	64	59	5	0.064
G2	37	29	8	
Recurrence (*n*)[a]				
Negative	86	80	6	<0.001*
Positive	12	6	6	

MPD main pancreatic duct

* Statistical significance at $P < 0.05$

[a] Patients who underwent complete resection were examined

identified as significant factors on univariate analysis, and all three factors ($P = 0.023$, $P = 0.009$, $P = 0.018$, respectively) appeared to be independent predictors for tumor recurrence on multivariate analysis.

Clinicopathological Correlation Study

To elucidate the radiology–pathology correlation, histology slides from the Kobe University cohort ($n = 51$) were reviewed. In this cohort, ten cases had MPD involvement. The pathological examination revealed that all ten tumors with MPD involvement exhibited an invasive growth pattern with fibrotic stroma. Entrapped MPDs were directly infiltrated by PNETs (Fig. 1b). Three cases (30%) also showed additional intraductal polypoid infiltration in the MPD (Fig. 1c). Microscopic venous

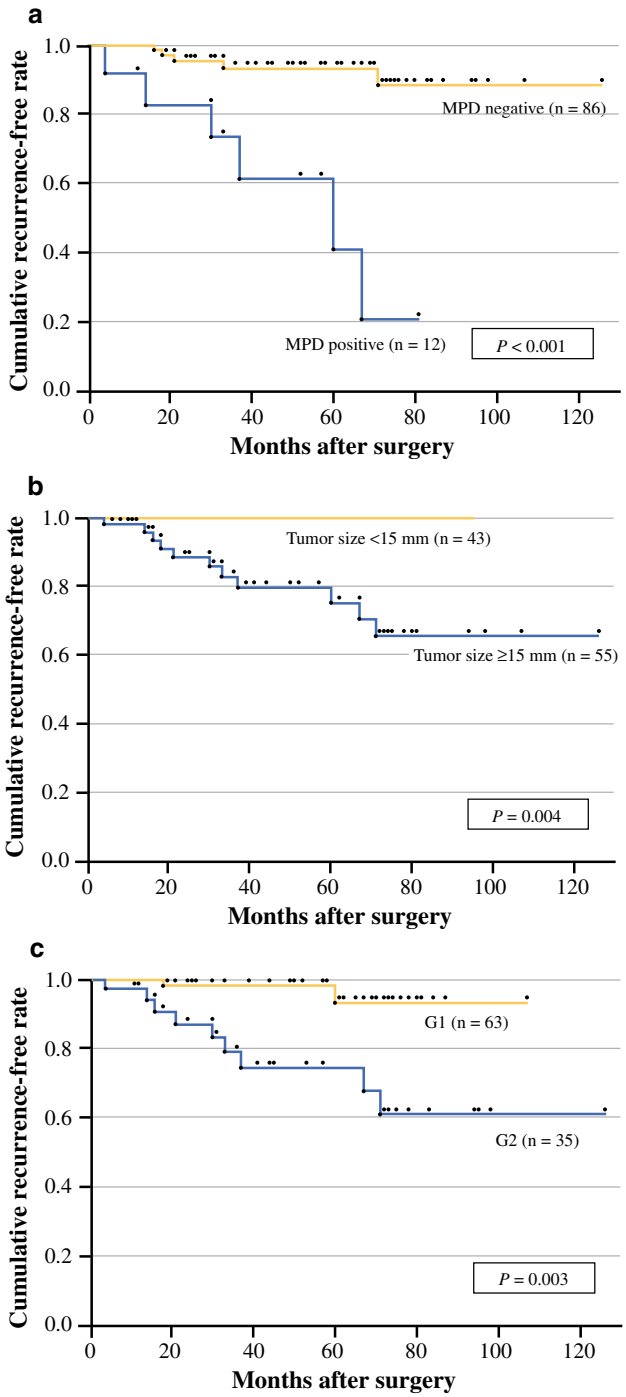

FIG. 2 Recurrence-free survival of patients with PNETs. Patients with MPD involvement (**a** $P < 0.001$ vs. no MPD involvement), tumor size ≥15 mm (**b** $P = 0.004$ vs. tumor size <15 mm), or G2 histological grade (**c** $P = 0.003$ vs. G1 histological grade) showed significantly worse recurrence-free survival. *PNET* pancreatic neuroendocrine tumor, *MPD* main pancreatic duct

TABLE 2 Uni- and multi-variate analyses for risk factors for nodal metastasis and recurrence

Variable	Nodal metastasis Positive/total	Univariate analysis		Multivariate analysis		Recurrence[a] Positive/total	Univariate analysis		Multivariate analysis	
		Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value		Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age										
<65 years	12/52	1.0 (Reference)	0.629			6/50	1.0 (Reference)	1.000		
≥65 years	9/49	0.75 (0.28–2.0)				6/48	1.0 (0.31–3.5)			
Sex										
Female	8/52	1.0 (Reference)	0.221			7/51	1.0 (Reference)	0.762		
Male	13/49	2.0 (0.74–5.3)				5/47	0.75 (0.22–2.5)			
Tumor size										
<15 mm	2/43	1.0 (Reference)	<0.001*	1.0 (Reference)	0.067	0/43	1.0 (Reference)	<0.001*	1.0 (Reference)	0.023*
≥15 mm	19/58	10 (2.2–46)		4.2 (0.91–30)		12/55	NA		NA	
Tumor location										
Head	8/37	1.00 (Reference)	1.000			5/37	1.0 (Reference)	0.761		
Body–tail	13/64	0.92 (0.34–2.5)				7/61	0.83 (0.24–2.8)			
Type of hormone production										
Non-functioning	19/76	1.0 (Reference)	0.090			11/73	1.0 (Reference)	0.286		
Functioning	2/25	0.26 (0.056–1.2)				1/25	0.23 (0.039–1.9)			
MPD involvement										
Negative	11/88	1.0 (Reference)	<0.001*	1.0 (Reference)	<0.001*	6/86	1.0 (Reference)	<0.001*	1.0 (Reference)	0.009*
Positive	10/13	23 (5.5–98)		16 (3.8–89)		6/12	13 (3.3–54)		8.0 (1.7–46)	
Histological classification										
G1	7/64	1.0 (Reference)	0.002*	1.00 (Reference)	0.093	2/63	1.0 (Reference)	<0.001*	1.0 (Reference)	0.018*
G2	14/37	5.0 (1.8–14)		2.9 (0.84–11)		10/35	12 (2.5–59)		6.7 (1.4–53)	

OR odds ratio, *CI* confidence interval, *NA* not available, *MPD* main pancreatic duct

* Statistical significance at $P < 0.05$

[a] 98 patients who underwent complete resection were examined

TABLE 3 Pathological and clinical details of the Kobe University cohort

Variable	Patients	MPD involvement		*P* value
	$n = 51$	Negative	Positive	
Venous invasion (*n*)				
Negative	30	28	2	0.010*
Positive	21	13	8	
Lymphatic invasion (*n*)				
Negative	41	33	8	1.000
Positive	10	8	2	
Perineural infiltration (*n*)				
Negative	41	37	4	0.002*
Positive	10	4	6	
Ki-67 index (*n*)				
≤2%	32	29	3	0.028*
>2%	19	12	7	
Mitotic count (*n*)				
<2 per 10 HPF	36	30	6	0.454
≥2 per 10 HPF	15	11	4	
Histological classification (*n*)				
G1	29	26	3	0.079
G2	22	15	7	
Serum pancreatic amylase level (U/L)				
Median (range)		34 (13–93)	55 (22–164)	0.018*
Serum lipase level (U/L)				
Median (range)		33 (10–65)	58 (28–197)	0.002*

MPD main pancreatic duct, *HPF* high-power field

* Statistical significance at $P < 0.05$

invasion and perineural infiltration were observed more commonly in PNETs with MPD involvement than in those without MPD involvement (Table 3). Although the Ki-67 index was higher in patients with MPD involvement than in those without MPD involvement [7/10 (70%) vs. 12/41 (30%), $P = 0.028$], the histological grade did not differ between the two groups ($P = 0.079$).

In terms of clinical and serological features, two patients with MPD involvement presented with abdominal pain, indicating pancreatitis. MPD involvement also was correlated significantly with higher preoperative serum concentrations of pancreatic amylase ($P = 0.018$) and lipase ($P = 0.002$; Table 3). However, no imaging features suggestive of severe acute pancreatitis, such as peripancreatic fluid correction, were observed in any of the patients.

DISCUSSION

Previous studies have not reached reliable conclusions regarding the clinical predictive factors for a progressive clinical course in patients with PNETs.[20–22] The present study revealed that MPD involvement in this uncommon pancreatic neoplasm is associated with multiple unfavorable clinical and pathological features. Most importantly, stricture of the MPD appeared to be an independent factor associated with nodal metastasis at the time of surgery and subsequent tumor recurrence during follow-up. Kaplan–Meier analysis also suggested that MPD involvement may be a stronger indicator of aggressive clinical behavior than large size (≥ 15 mm) or G2 PNETs, given that the 5 years recurrence-free rate of PNETs with MPD involvement was just 41%.

Although the biological nature of MPD involvement in PNETs remains elusive, MPD involvement in PNETs may relate to a unique growth pattern.[15,16,23–26] Unlike classic PNETs, which proliferate in a medullary pattern with scant stroma, PNETs with MPD involvement appeared to be more fibrotic and infiltrative into adjacent structures, which is likely the reason that the MPD is entrapped inside the tumor masses. Therefore, a sign of MPD involvement on imaging may be a good indicator of an infiltrative histological growth pattern. Previous studies have shown that a subset of PNETs produce multiple tumor-related growth factors (e.g., platelet-derived growth factor, transforming growth factor-beta, and basic fibroblast growth factor), and they are suspected to stimulate a fibroblastic reaction and vascularization.[25,26] These factors may be involved in the infiltrative growth and development of the fibrotic stroma in PNETs with MPD involvement.

Several studies have suggested that nodal metastasis of PNETs is related to shorter disease-related survival and that regional lymph node dissection may decrease the risk of locoregional tumor recurrence.[2,4,27,28] However, it remains difficult to determine whether nodal dissection is truly necessary on a case-by-case basis in clinical practice. In this study, more than half of the cases with MPD involvement had nodal metastases, suggesting that regional lymph node dissection should be considered in PNET cases with MPD involvement. Similarly, given the high risk of tumor recurrence in patients with PNETs involving the MPD, close follow-up also is required for such patients. To the best of our knowledge, no imaging features that reliably predict the biological behavior of PNETs have been determined. MPD involvement in PNETs will be an easy-to-assess, reproducible imaging finding suggestive of aggressive clinical behaviors.

This study has several limitations. First, only surgical cases were examined. Second, standard lymph node dissection was not completed in all cases; regional lymph nodes were removed in 72% of the nonfunctioning tumors and 44% of the functioning tumors. Third, the follow-up period (median 43 months; range 2–133 months) may not be long enough for slow-growing tumors like PNETs. Finally, the MPD involvement in cases of pancreatic body-

tail tumors might be underestimated, because distal duct dilatation is suspected to be less apparent.

CONCLUSIONS

The results of the current study suggest that MPD involvement in PNETs may be a useful imaging sign, indicating an aggressive clinical course, such as nodal metastasis and tumor recurrence. This is probably because MPD involvement is linked to a histological infiltrative growth pattern. Regional lymph node dissection and long-time follow-up will be required in patients with resectable PNETs with MPD involvement.

DISCLOSURES All authors have no conflicts of interest and nothing to disclose.

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