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Pancreatic insufficiency following pancreatectomy: Does underlying tumor syndrome confer a greater risk?☆

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Abstract

Background: The risk of postoperative pancreatic exocrine insufficiency (PPEI) is unknown in patients with multiple endocrine neoplasia type I (MEN1) and von Hippel-Lindau (VHL) who require resection of pancreatic neuroendocrine tumors (PNETs).

Methods: A retrospective review of patients who underwent resection of PNETs at the National Institutes of Health from 2007 to 2019 was performed.

Results: Our cohort included 82 patients (VHL n = 25, MEN1 n = 20, sporadic n = 37), 6 of whom developed PPEI. While VHL compared to all non-VHL patients ($p = 0.046$), non-functional PNETs ($p = 0.050$), and pancreaticoduodenectomy (PD) (p=<0.001) were associated with higher rates of PPEI on univariate analysis, only PD was found to be an independent predictor of PPEI on multivariate analysis (OR 14.43, 95% CI 1.43–145.8, $p = 0.024$).

Conclusions: The rate of PPEI in patients with hereditary tumor syndromes was similar to that of sporadic PNETs. PD was independently associated with PPEI, and this increased risk should be included in preoperative counseling.

Keywords

MEN-1; VHL; Pancreatectomy; Pancreatic insufficiency

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Contributions

I. Conception and design: McDonald, Gupta, Shindorf, Copeland, Good, Nilubol.

II. Collection and assembly of data: McDonald, Gupta, Shindorf, Copeland, Good.

III. Data analysis: McDonald, Nilubol.

IV. Manuscript writing: McDonald, Gupta, Shindorf, Copeland, Good, Sadowski, Nilubol.

Declaration of competing interest

There are no conflicts of interest to disclose.

1. Introduction

Patients with multiple endocrine neoplasia type I syndrome (MEN1) and von Hippel-Lindau disease (VHL) frequently develop pancreatic manifestations of their disease. In MEN1, up to 70% of patients will develop pancreatic neuroendocrine tumors (PNETs) both functional and non-functional.[1,2] In VHL, up to 70% of patients will have pancreatic cysts and as high as 17% will have PNETs.[3–7] The risk of metastasis in these patient populations is primarily attributed to the size and the rate of growth.[3,8] Hence, current guidelines recommend surgical resection of PNETs >2 cm in patients with MEN1 and resection of tumors >2 cm and >3 cm, in the head and body/tail of the pancreas respectively, for patients with VHL.[3,8–10] In addition to the high prevalence of PNETs in patients with MEN1 and VHL, patients commonly present with multiple PNETs and, in the case of VHL, often have PNETs in the setting of a polycystic pancreas.[11] This is an important distinction when considering surgical resection in these patients because the surgeon must be cognizant of the volume of functional remnant pancreas after resection and the potential for both exocrine and endocrine insufficiency following surgery.

Previous studies that evaluated complications following pancreatectomy, demonstrated higher rates of postoperative pancreatic exocrine insufficiency (PPEI) in patients who underwent pancreatic duodenectomy (PD) compared distal pancreatectomy (DP), as well as in patients with a lower BMI, a history of acute pancreatitis, and those patients with an obstructive pathology or elevated preoperative bilirubin.[12,13] This data, however, may not be representative of patients with MEN1 or VHL who undergo pancreatic resection as these cohorts included all patients who underwent pancreatic resection and did not specify whether patients with MEN1 or VHL were included.

Although MEN1 and VHL are rare diseases and seen less frequently than other pathologies, these patients will frequently undergo pancreatic resection and sometimes multiple pancreatic resections in their lifetime and data on the rate of PPEI and other complications following pancreatectomy in this population is scarce. This study aimed to compare a cohort of patients with VHL, MEN1, and sporadic PNETs who underwent pancreatectomy at a single institution. We sought to examine which factors were associated with the development of PPEI and determine where a difference exists between the rate of PPEI among these groups. We hypothesized that patients with VHL, due to the high rate of cystic disease and therefore decreased residual functional pancreas following resection, would be more likely to develop PPEI following pancreatectomy for PNETs compared to patients with MEN1-related PNETs and sporadic PNETs.

2. Methods

2.1. Data source and cohort selection

We performed a retrospective analysis of a prospectively maintained data set of patients who underwent pancreatectomy for PNETs at the National Institutes of Health (NIH) between 2007 and 2019. Patients were excluded if they had undergone a prior pancreatic resection, underwent a total or completion pancreatectomy, or if they underwent pancreatectomy for a diagnosis other than PNET. This study was approved by the Office for Human Research

Protections, The U.S.Department of Health and Human Services. All patients provided written consent.

2.2. Demographics and patient characteristics

Data were obtained from a review of patient medical records. The diagnoses of MEN1 and VHL are made by previously published criteria.[14,15] Demographic and clinical variables of interest included age, gender, BMI, underlying diagnosis (VHL, MEN1, sporadic, other), the presence of a cystic pancreas, prior pancreatic resection, history of pancreatitis, a documented history of alcohol abuse or smoking, preoperative diabetes mellitus, and preoperative exocrine replacement therapy. Perioperative variables of interest included surgical procedure performed, the volume of pancreas resected, the presence of multifocal PNETs, tumor grade as defined by the WHO 2017 criteria, histologic-proven metastasis, functional status of PNETs, the presence of cysts and/or PNETs in the remnant pancreas, post-operative exocrine replacement as defined by the requirement of pancreatic enzyme replacement postoperatively based on patient-reported characteristic symptoms with or without positive fecal fat and the improvement of symptoms following pancreatic enzyme replacement, new or worsening diabetes as defined the initiation or the increased requirement of glucose control medications, and length of follow up. Age, BMI, volume of pancreas resected, and length of follow up were recorded as continuous variables and all other variables were recorded as categorical.

Surgical and pathologic characteristics were obtained from a review of the operative reports, intraoperative nursing and anesthesia documentation, and final pathology reports. The total volume of pancreas resected was determined from the final pathology report and calculated using the equation for the volume of an eliopsoid $\left(volume = \pi/6 \sum_{i=1}^{n} (lwh)_i\right)$.[16]

2.3. Statistical analysis

An initial analysis was performed to determine baseline differences in the three groups in Table 1, and also differences in those patients who developed PPEI and those who did not (Table 2). χ^2 tests were performed on all categorical variables and for continuous variables that were normally distributed, a Student's T-test was performed, and for those without a normal distribution, the Mann-Whitney U test was performed.[17,18] In order to determine which factors were independently associated with the development of PPEI, a univariate and multivariate Cox proportional hazard regression modeling were performed.[19] Variables with P values ≤ 0.10 in univariate analyses for post-operative exocrine replacement were included in the multivariable anaylsis. Two-tailed $P < 0.05$ was considered statistically significant. Smoking history, history of pancreatitis, history of alcohol abuse, and history of preoperative diabetes were excluded from the univariate analysis because no patients who were positive for those factors also developed PPEI. All statistical analyses were calculated with IBM SPSS software, Windows version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographics and preoperative patient characteristics

Eighty-two patients were included in our analysis. The median age was 46 years (interquartile range (IQR) 35–60), more than half were female, and the median BMI was 30 kg/m^2 (IQR 25–33 kg/m^2). The majority of patients (45/82) in our cohort had underlying familial tumor syndromes. VHL and MEN1 were similarly represented with 25 and 20 patients, respectively and the remaining 37 patients had sporadic tumors. Nearly a quarter of patients had cystic pancreas preoperatively (Sporadic 3/37, MEN1 2/20, and VHL 15/25). Three patients had a history of pancreatitis, and 6 had a history of alcohol abuse. No patients had preoperative pancreatic exocrine insufficiency (PEI) as reported in the medical record.

3.2. Surgical, pathologic, and perioperative features

In our cohort, 39 patients underwent enucleation. Thirty-seven and 6 patients underwent distal pancreatectomy and PD, respectively. The median volume of pancreas resected was 18 cm^3 (IQR 2.3–51.8 cm^3), and 37 patients had multifocal tumors (sporadic n = 6, MEN1 n-17, and VHL n = 14). Following resection, 17 patients had cysts and 31 patients had additional PNETs involving the remnant pancreas. Half of the tumors resected were functional, all but two patients had tumors that were WHO Grade 2 or 3, and 12 of 82 were metastatic at the time of surgery. Postoperatively 6 patients developed PPEI and 14 had new or worsening DM. The median follow-up in our cohort was 639 days (IQR 22–1897 days). The clinical and pathologic features are displayed for our overall cohort, as well as subdivided by underlying pathology (Table 1).

3.3. Characteristics of patients who developed PPEI

When a comparison of between the patients who developed PPEI and those who did not was performed (Table 2), we found an increased rate of PPEI in patients with VHL compared to Non-VHL patients ($p = 0.015$), patients with non-functional PNETS ($p = 0.05$), and those patients who underwent a PD ($p = < 0.001$).

3.4. Factors associated with the development of PPEI

To determine which factors were associated with the development of PPEI, a univariate and multivariable analysis was performed (Table 3). Factors with a p-values ≤0.100 on the univariate analysis were then put into a Cox multivariable hazard model. Of the 3 variables (VHL vs. VHL, Functional Tumor, and Surgical Procedure), only PD was independently associated with the development of PPEI on multivariable analysis [$p = 0.009$, OR 21.01 (95% CI 2.163–203.958)].

4. Discussion

This is the first study comparing rates of PPEI following pancreatectomy in patients with VHL and MEN1 compared to patients with sporadic PNETs. We hypothesized that patients with VHL would experience PPEI at a higher rate than patients with MEN1 and patients with sporadic PNETs due to the high frequency of polycystic pancreas in patients with VHL. While we did observe a higher rate of PPEI in VHL versus non-VHL patients, patients with

non-functional tumors, and those patients who underwent pancreaticoduodenectomy, only PD was found to be an independent predictor of developing PPEI on multivariable analysis. Although there are likely other factors associated with the development of PPEI in this group of patients, with such a small number of events (n = 6) occurring in our series analysis using a larger cohort is necessary to detect these differences between the groups.

PPEI following pancreatectomy has been reported as high as 41% for PD and 12–20% for DP in large recently published studies, but these series analyzed all patients who underwent pancreatectomy for a variety of indications.[12,13] While this data is useful, these studies did not control for patients with underlying syndromes such as VHL or MEN1. Although 4/25 (16%) of patients with VHL who underwent pancreatectomy developed PPEI, historical data to compare this number to are scarce.[20] Furthermore, our rates of PPEI were lower than what has been previously reported for pancreatectomy in the setting of MEN1 (3.8% vs 10%).[20] The difference in the rates of PPEI in our series compared to recent studies that looked at all-comers undergoing pancreatectomy emphasizes the importance of identifying the true rate of PPEI for patients with hereditary syndromes, as they are more likely to require a pancreatectomy in their lifetime than the general population.

Risk factors for PPEI following pancreatectomy that have been identified in the literature include low BMI, history of pancreatitis, obstructive pathology or elevated preoperative bilirubin, and PD.[12,13,20] However, in our series we found PD to be the only factor independently associated with the development of PPEI. One reason for the discrepancy could be that our cohort is a highly selected group who all underwent resection for PNETs as compared to other studies, which included patients who underwent pancreatectomy for a variety of pathologies. In fact, other studies included patients who underwent pancreatectomy in the setting of chronic pancreatitis, a group that would be considered high risk for the development of PPEI and could be one of the reasons why rates in the literature are higher than that of our cohort. When comparing the findings from our study to the reported data, fewer factors returned with significance than what has been previously seen. This is likely because our single-center cohort comprised rare diseases with a smaller sample size and a low rate of PPEI that may result in a Type II error. A larger cohort through a collaboration with other high volume MEN1 and VHL centers can increase the power to detect the differences in other variables.

There are several key features of this study that are relevant to the surveillance and surgical intervention in patients with VHL and MEN1. Current recommendations for resection of PNETs in patients with VHL and MEN1 are based on tumor size, growth rate, and location.[3,8–10] While these recommendations for resection of PNETs are made to guide the removal of those tumors harboring the highest risk of malignancy, a consideration should be made to preserve pancreatic parenchyma while achieving adequate tumor control. Our data demonstrate that the development of PPEI was associated with the type of resection performed rather than the diagnosis for which it was indicated. Although a larger cohort is necessary to make further statements about the risk factors for PPEI in patients with MEN1 and VHL, an argument could be made to broaden the resection criteria to target smaller lesions while they are still amendable to a limited resection with improved pancreatic preservation.

There are several limitations to this study. First and foremost, this was a retrospective study with inherent selection biases and limitations. However, all patients with VHL and MEN1 received a standardized surveillance program and the indication of surgical intervention based on the risk of PNET metastasis in VHL and MEN1.[7,21] Next, although our study is one of the only reports in the literature to control for volume of pancreas resected as well as the type of resection performed, it does lacks data regarding the volume of remnant pancreas remaining as well as the proportion of cyst and PNET involvement in the remnant. A prospective study with specific imaging protocols would be necessary to adequately assess volume and make-up of the remnant pancreas in this group. In addition to these, the relatively short duration of follow-up in the sporadic group compared to MEN1 and VHL like results in underreporting of PPEI in the sporadic cohort. Another limitation of our study was that the diagnosis of PPEI was made based on patient symptoms and the resolution of symptoms with pancreatic enzyme replacement therapy. Thus, the rate of PPEI may be underreported because the fecal fat testing was not routinely performed. Finally, although this cohort would be considered large for such a rare disease, the power of the study and potentially the ability to parse out all the factors that contribute to the development of PPEI in patients with VHL and MEN1 who undergo pancreatectomy is limited by the number of patients as well as the small number of events which may also explain some of the differences seen on univariate analysis.

5. Conclusions

The rate of PPEI in patients with hereditary tumor syndromes was not significantly different than that of sporadic PNETs. Because PD was independently associated with PPEI, it should be routinely included in preoperative counseling.

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Table 1

Clinicopathologic characteristics.

	OVERALL (n = 82)	SPORADIC (n = 37)	MEN1 (n = 20)	VHL (n = 25)	*P*
Median Age (IQR)	46 (35–60)	57 (43–63)	40 (29–49)	43 (35–53)	**0.003**
Gender					0.90
Male	40	19	9	12	
Female	42	18	11	13	
Median BMI (IQR)	30 (25–33)	22 (25–34)	29 (26–32)	31 (24–33)	0.98
Underlying Diagnosis					–
Sporadic	37	37	0	0	
MEN1	20	0	20	0	
VHL	25	0	0	25	
VHL v Non-VHL					
Non-VHL	57				
VHL	25				
Familial v Sporadic					
Sporadic	37				
Familial	45				
Cystic Pancreas					**< 0.001**
No	62	34	18	10	
Yes	20	3	2	15	
Functional Tumor					**< 0.001**
No	37	3	9	25	
Yes	45	34	11	0	
History of Pancreatitis					0.19
No	79	36	18	25	

	OVERALL	SPORADIC	MEN1	VHL	*P*
	(n = 82)	(n = 37)	(n = 20)	(n = 25)	
Yes	3	1	2	0	
History of Alcohol Abuse					0.14
No	75	35	19	21	
Yes	6	1	1	4	
History of Smoking					0.06
No	59	28	17	14	
Yes	22	8	3	11	
Pre-Op Diabetes					0.78
No	72	33	18	21	
Yes	10	4	2	4	
Pre-op Exocrine Replacement					–
No	82	37	20	25	
Yes	0	0	0	0	
Surgical Procedure					**0.005**
Enucleation	39	24	4	11	
Distal Pancreatectomy	37	12	15	10	
Pancreatiocoduodenectomy	6	1	1	4	
Volume of Pancreas Resected					0.65
Mean (range)	33 cm^3 (0.02–397 cm^3)	28 cm^3 (0.02–397 cm^3)	42 cm^3 (2–174 cm^3)	32 cm^3 (0.87–123 cm^3)	
Median (IQR)	18 cm^3 (2–52 cm^3)	2 cm^3 (0.40–24 cm^3)	32 cm^3 (8–61 cm^3)	19 cm^3 (4–51 cm^3)	
Multifocal					**0.001**
No	52	31	7	14	
Yes	30	6	13	11	
Tumor Grade					0.16
Grade 1	43	22	12	9	
Grade 2	21	5	6	10	

	OVERALL	SPORADIC	MEN1	VHL	*P*
	(n = 82)	**(n = 37)**	**(n = 20)**	**(n = 25)**	
Grade 3	2	1	0	1	
Metastasis					0.22
No	70	34	15	21	
Yes	12	3	5	4	
Cysts in remnant pancreas					**< 0.001**
No	67	34	18	10	
Yes	15	3	2	15	
PNET in remnant pancreas					**< 0.001**
No	57	35	9	13	
Yes	25	2	11	12	
Post-op Exocrine Replacement					0.13
No	76	36	19	21	
Yes	6	1	1	4	
>New or Worsening Diabetes					
No	72	35	16	21	0.22
Yes	10	2	4	4	
Median Length of Days Follow Up (IQR)	629 (15–1894)	22 (0–177)	1454 (442–2271)	1863(648–2826)	**< 0.001**

MEN1: multiple endocrine neoplasia type 1,VHL: von Hippel-Lindau, PNET: pancreatic neuroendocrine tumor.

** Three patients underwent enucleation, 5 underwent DP, and 1 underwent PD.

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Table 2

Comparison of clinicopathologic features by post-operative exocrine replacement.

	Post-operative Pancreatic Exocrine Insufficiency		
	No	Yes	*P*
	(n = 76)	(n = 6)	
Median Age (IQR)	46 (35–60)	47 (44–53)	0.80
Gender			0.62
Male	38	2	
Female	38	4	
Median BMI (IQR)	29 (25–33)	30 (22–40)	0.78
Underlying Diagnosis			0.13
Sporadic	36	1	
MEN1	19	1	
VHL	21	4	
VHL v Non-VHL			**0.046**
Non-VHL	55	2	
VHL	21	4	
Familial v Sporadic			0.15
Sporadic	55	2	
Familial	21	4	
Cystic Pancreas			0.60
No	58	4	
Yes	18	2	
Functional Tumor			**0.05**
No	32	5	
Yes	44	1	
History of Pancreatitis			0.62

	Post-operative Pancreatic Exocrine Insufficiency		
	No	Yes	*P*
	(n = 76)	(n = 6)	
No	73	6	
Yes	3	0	
History of Alcohol Abuse			0.47
No	69	6	
Yes	6	0	
History of Smoking			0.12
No	53	6	
Yes	22	0	
Pre-Op Diabetes			0.34
No	66	6	
Yes	10	0	
Surgical Procedure			**< 0.001**
Enucleation	37	2	
Distal Pancreatectomy	36	1	
Pancreatiocoduodenectomy	3	3	
Volume of Pancreas Resected			0.30
Mean (Range)	31 cm^3 (0.02–397 cm^3)	55 cm^3 (5–119 cm^3)	
Median (IQR)	10 cm^3 (2–52 cm^3)	47 cm^3 (44–66 cm^3)	
Multifocal			0.48
No	49	3	
Yes	27	3	
Tumor Grade			0.86
Grade 1	40	3	
Grade 2	19	2	
Grade 3	2	0	

	Post-operative Pancreatic Exocrine Insufficiency		
	No	Yes	*P*
	(n = 76)	(n = 6)	
Metastasis			0.18
No	66	4	
Yes	10	2	
Cysts in remnant pancreas			0.32
No	63	4	
Yes	13	2	
PNET in remnant pancreas			0.45
No	52	5	
Yes	24	1	
New or Worsening Diabetes			0.73
No	67	5	
Yes	9	1	
Median Length of Days Follow Up (IQR)	571 (12–1784)	2503(581–3025)	0.11

Table 3

Univariate and multivariable analysis of factors associated with PPEI.

Variable	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Age	0.99	0.94–1.05	0.82			
Gender						
Male	Ref					
Female	2.00	0.35–11.58	0.44			
BMI	1.02	0.91–1.13	0.78			
VHL vs Non-VHL						
Non-VHL	Ref			Ref		
VHL	5.24	0.89–30.76	0.07	0.32	0.01–8.53	0.50
Cystic Pancreas						
No	Ref					
Yes	1.61	0.27–9.53	0.60			
Functional Tumor						
No	Ref			Ref		
Yes	0.15	0.02–1.31	0.09	0.05	0.001–2.01	0.11
Surgical Procedure						
Enucleation	Ref			Ref		
Distal Pancreatectomy	0.51	0.05–5.92	0.59	0.18	0.01 –4.29	0.29
Pancreatiocoduodenectomy	18.50	2.17–157.46	**0.008**	14.43	1.43–145.76	**0.024**
Volume of Pancreas Resected	1.01	0.99–1.02	0.33			
Multifocal						
No	Ref					
Yes	1.82	0.34–9.62	0.48			
Tumor Grade						

Variable	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Grade 1	Ref					
Grade 2	1.40	0.22–9.11	0.50			
Grade 3 *	-	-	-			
Metastasis						
No	Ref					
Yes	3.30	0.53–20.43	0.20			
Cysts in remnant pancreas						
No	Ref					
Yes	2.42	0.40–14.65	0.34			
PNET in remnant pancreas						
No	Ref					
Yes	0.43	0.05–3.91	0.46			
New or Worsening DM						
No	Ref					
Yes	1.49	0.16–14.23	0.73			

MEN1: multiple endocrine neoplasia type 1, VHL: von Hippel-Lindau, PPEI: postoperative exocrine insufficiency.

* No cases of PPEI for Grade 3 tumors.