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Risk factors for complications after surgery for pancreatic neuroendocrine tumors

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ABSTRACT

Background: Surgical resection is the only potentially curative treatment for pancreatic neuroendocrine tumors. The choice for the type of procedure is influenced by the expected oncological benefit and the anticipated risk of procedure-specific complications. Few studies have focused on complications in these patients. This cohort study aimed to assess complications and risk factors after resections of pancreatic neuroendocrine tumors.

Methods: Patients undergoing resection of a pancreatic neuroendocrine tumor were identified within 2 centers of excellence. Complications were assessed according to the Clavien-Dindo classification and the comprehensive complication index. Logistic regression was performed to compare surgical procedures with adjustment for potential confounders (Clavien-Dindo ≥3).

Results: The cohort comprised 123 patients, including 12 enucleations, 50 distal pancreatectomies, 51 pancreatoduodenectomies, and 10 total/combined pancreatectomies. Mortality was 0.8%, a severe complication occurred in 41.5%, and the failure-to-rescue rate was 2.0%. The median comprehensive complication index was 22.6 (0–100); the comprehensive complication index increased after more extensive resections. After adjustment, a pancreatoduodenectomy, as compared to a distal pancreatectomy, increased the risk for a severe complication (odds ratio 3.13 [95% confidence interval 1.32–7.41]). Of the patients with multiple endocrine neoplasia type 1 or von Hippel-Lindau, 51.9% developed a severe complication vs 38.5% with sporadic disease. After major resections, morbidity was significantly higher in patients with multiple endocrine neoplasia type 1/von Hippel-Lindau (comprehensive complication index 45.1 vs 28.9, $P = .029$).

Conclusion: Surgery for pancreatic neuroendocrine tumors is associated with a high rate of complications but low failure-to-rescue in centers of excellence. Complications are procedure-specific. Major resections in patients with multiple endocrine neoplasia type 1/von Hippel-Lindau appear to increase the risk of complications.

Introduction

Pancreatic neuroendocrine tumors (pNETs) have an estimated incidence of less than 1 per 100,000 persons, but their incidence is rising.[1–3] Less than 10% of all pancreatic operations and only 2.7% to 6.3% of the pancreatoduodenectomies are performed for pNETs.[4,5]

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Less than 1 in 10 occurs in a familial fashion, predominantly multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease (VHL).[6] When the peptides secreted by the pNET induce symptoms, the tumor is regarded as a functioning pNET (F-pNET); all others are considered as non-functioning (NF-pNETs).

Surgical resection is the cornerstone of curative treatment and is increasingly performed for pNETs.[7] The European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society guidelines recommend operative resection of F-pNETs, irrespective of their size.[8,9] Both guidelines recommend resection of NF-pNETs larger than 2 cm but suggest that surgical resections could also be considered for NF-pNETs less than 2 cm.[8,9] The decision to proceed to surgical resection and the choice for the type of procedure are influenced by the expected oncological benefit and the anticipated risk of procedure-specific complications.

Data on complications after pancreatic resections are abundant, but published data specifically on complication rates after pancreatic surgery for pNETs are limited. Patients with pNETs also undergo atypical pancreatic resections, have a soft pancreas and non-dilated pancreatic duct, which increase the risk of complications.[10−13] Most studies that incldued at least 100 patients with resected pNETs focused on postoperative pancreatic fistula (POPF), whereas patients are at risk for other pancreatic and general surgery-related complications as well. In these studies, patients have been included over almost 2 decades,[13−17] mainly before 2010,[14−19] and specific inclusion criteria have been applied based on size or metastases,[15,19] functionality[16,17], MEN1,[20,21] or sporadic nature,[14] thereby limiting the applicability of these studies during patient counseling in general practice. Besides, most studies lacked a detailed and comprehensive assessment and grading of complications according to accepted criteria, and risk factors are largely unknown.[15−19,22,23] This study aimed to assess procedure-specific complications and risk factors for complications after operations for pNETs in 2 ENETS Centers Of Excellence. The secondary aims were to compare postoperative complications of patients with (multifocal) MEN/VHL-related with (solitary) sporadic pNETs and those with F-pNETs versus NF-pNETs.

Methods

Study design

Patients who underwent resection of a histopathologically proven pNET between 2008 and 2019 at the University Medical Center Utrecht (UMCU) and University Medical Center Groningen (UMCG) were identified retrospectively by extensive review of the surgical procedures database and histopathological archives. Both centers are high-volume centers for pancreatic surgery—defined as at least 20 pancreatoduodenectomies annually in the Netherlands[24]—and are specialized in pNETs. Both are certified as ENETS Center of Excellence. Patients were identified by an extensive search of the pathology reports and review of the surgical procedures databases. Patients undergoing pancreatic resections for a duodenal NET were not eligible. The study was approved by medical ethics committees from both centers (Research Register number 201900734 [UMCG] and 19/670 [UMCU]).

Clinical definitions

Data regarding patient demographics, work-up, operation, postoperative complications, and follow-up were collected from the electronic patient records. No data were collected on race/ethnicity. Tumors without distinct clinical symptoms caused by excessive hormone excretion were regarded as NF-pNETs. Tumors were considered as F-pNET in case of excessive hormone production leading to distinct clinical symptoms and referred to as insulinomas, gastrinomas, glucagonomas, and somatostatinomas, depending on the respective hormone secreted.

The presence of MEN1 or VHL disease was assessed per clinical practice guidelines or statements.[25,26] Length of hospital stay (LOS) was calculated from the date of resection until the date of discharge. Readmission was defined as an admission after initial discharge for a complication within 30 days.

Preoperative tumor size of the largest pNET was based on the maximum observed size on conventional imaging. If conventional or functional imaging was positive for local lymph node or liver metastases, the patient was considered as having the respective metastases.

Surgery

Surgical indications and strategies were based on multidisciplinary team discussions and intraoperative findings. In both centers, surgical procedures were performed in teams of surgeons with vast competence in pancreatic surgery and experience in pNETs. An enucleation was defined as a local resection of a pNET without the resection of surrounding tissue. Pancreatoduodenectomies considered Whipple procedures and pylorus-preserving pancreatoduodenectomies (PPPD). Combined resections, eg, Whipple/PPPD and distal pancreatectomy (DP), were reserved for patients with multifocal tumors occurring in MEN1/VHL disease. To be classified as a Whipple/PPPD plus DP, preservation of at least a part of the pancreatic body or tail was demanded.[21] No central pancreatectomies were performed. Enucleations and DP were regarded as minor resections and Whipple/PPPDs, and total and combined pancreatectomies were considered as major resections.

Outcome measures and definitions

Postoperative complications within 30 days after surgical resection or during hospitalization were graded according to the Clavien-Dindo classification.[27] The primary outcome of the study was the occurrence of a severe postoperative complication (Clavien-Dindo $\geq$3).[27] Mortality included deaths within 90 days.

The cumulative burden of complications was expressed as the comprehensive complication index (CCI), which is calculated as the sum of all complications weighted for their severity and expressed on a continuous scale ranging from 0 (no complication) to 100 (death).[28,29] The CCI scores were used to calculate estimated costs, in Euros and United States dollars, based on the type of resection, age, and CCI.[30] A cumulative CCI of $\geq$37.1, which reflects the burden of at least 2 Clavien-Dindo grade 3a complications, was previously used to determine high morbidity due to operative complications.[31]

Secondary outcomes included the presence and severity of pancreatic surgery-associated complications—POPF, delayed gastric emptying (DGE), post-pancreatectomy hemorrhage (PPH), bile leak, and chyle leak—which were assessed and graded according to definitions and criteria formulated by the International Study Group of Pancreatic Surgery (ISGPS).[32−36] Grade B/C complications were considered clinically relevant. Patients with a total pancreatectomy were excluded from the POPF analysis. For the analysis of bile leak, only patients undergoing resection of the pancreatic head (Whipple/PPPD, total pancreatectomy, or enucleation of the pancreatic head) were included. Failure-to-rescue was defined as death due to a severe complication.[37]

Statistical analysis

Continuous variables were presented as mean ($\pm$ standard deviation) or as median (range). Categorical variables were presented as count (percentage). Differences in continuous variables were assessed using Mann-Whitney *U* or Kruskal Wallis tests, and categorical data were compared by using χ^2 analysis or Fisher exact test. Differences in characteristics were compared between patients with MEN1/VHL versus those with sporadic disease and patients with a NF-pNET versus those with a F-pNET, respectively.

Severe complications, ISGPS grade B/C complications, and CCI with estimated associated costs were compared between different surgical procedures (enucleation versus DP versus Whipple/PPPD versus total/combined pancreatectomy), patients with MEN1/VHL versus sporadic disease, and F-pNETs versus NF-pNETs. The analyses were stratified by the extent of resection.

The potential associations between preoperative characteristics and the occurrence of a severe complication or POPF were assessed using univariable logistic regression providing odds ratios (OR) with corresponding 95% confidence intervals (CI). Variables evaluated for an association with a severe complication were age at surgery in years, sex, American Society of Anesthesiologists (ASA) score, type of pancreatic resection, type of pNET, MEN1/VHL, radiological size in mm, radiological pNET ≥2 cm, radiological lymph node metastases, radiological liver metastases, and surgical approach. The same variables were analyzed for an association with a POPF.

In multivariable analysis, the effect of surgical procedures was adjusted for age at surgery, ASA score, pNET functionality, and presence of a radiological pNET ≥2 cm, based on clinical experience and reasoning. Because only a limited number of covariates could be adjusted for, we performed sensitivity analyses by including different combinations of covariates.

Missing data were considered missing at random and therefore imputed using multiple imputation with the iterative Markov chain Monte Carlo method, creating 20 datasets.[38,39] Variables listed in Table I, as well as hospital, solitary, or multiple radiological pNETs, and the period of operation (before and in 2014 or later), and the occurrence of a severe complication, were used as predictor variables for multiple imputation. For the POPF analysis, POPF was included as the outcome for imputation. Odds ratios and 95% CI were pooled using Rubin's rules.[40] Data were analyzed using SPSS version 25.0 (IBM Corp, New York, NY) and R version 3.5.1 with 'Mice' package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

In total, 123 patients were included with a mean age of 54 (±14) years (Table II). Sixty-four were female patients (52%), and 27 (21.9%) patients had a genetic syndrome. In 25 patients, MEN1 or VHL was confirmed by genetic testing; in 1 patient fulfilling clinical criteria, no mutation was found by genetical testing, and in 1 patient, it was unclear whether genetic testing was performed. The latter patient fulfilled clinical criteria and had a proven mutation

Table I
Risk factors for a severe complication

	Severe complication*		Univariable analysis		Multivariable analysis	
	Yes n = 51 (41.5%)	No n = 72 (58.5%)	Crude OR	95% CI	Adjusted OR	95% CI
Age surgery in years†	55 (18–81)	56 (6–77)	1.00	0.97–1.03	1.00	0.97–1.03
Sex					–	–
Female	23 (45.1%)	41 (56.9%)	1	Ref.		
Male	28 (54.9%)	31 (43.1%)	1.61	0.78–3.34		
ASA grade						
ASA 1 or 2	39 (76.5%)	61 (84.7%)	1	Ref.	1	Ref.
ASA 3 or 4	12 (23.5%)	11 (15.3%)	1.71	0.68–4.29	1.51	0.56–4.04
Pancreatic resection						
Distal pancreatectomy	16 (31.4%)	34 (47.2%)	1	Ref.	1	Ref.
Enucleation	1 (2.0%)	11 (15.3%)	0.19	0.02–1.66	0.19	0.02–1.73
Whipple/PPPD	29 (56.9%)	22 (30.6%)	2.80	1.23–6.37	3.13	1.32–7.41
Total or other	5 (9.8%)	5 (6.9%)	2.13	0.53–8.52	2.14	0.50–9.11
Type of tumor						
NF-pNET	35 (68.6%)	52 (72.2%)	1	Ref.	1	Ref.
F-pNET	16 (31.4%)	20 (27.8%)	1.19	0.54–2.63	1.59	0.59–4.26
Hereditary syndrome					–	–
Absent	37 (72.5%)	59 (81.9%)	1	Ref.		
Present	14 (27.5%)	13 (18.1%)	1.72	0.72–4.09		
Size imaging in mm	23 (6–140)	24 (8–140)	0.99	0.98–1.01	–	–
pNET ≥ 2 cm						
Absent	20 (39.2%)	28 (38.9%)	1	Ref.	1	Ref.
Present	31 (60.8%)	44 (61.1%)	1.01	0.47–2.17	0.98	0.38–2.55
Lymph node metastases					–	–
Absent	37 (72.5%)	56 (77.8%)	1	Ref.		
Present	14 (27.5%)	16 (22.2%)	1.31	0.57–3.04		
Liver metastases					–	–
Absent	40 (78.4%)	61 (84.7%)	1	Ref.		
Present	11 (21.6%)	11 (15.3%)	1.50	0.59–3.83		
Approach					–	–
Open	37 (72.5%)	45 (62.5%)	1	Ref.		
Laparoscopic	4 (7.8%)	12 (16.7%)	0.41	0.12–1.38		
Robot-assisted	10 (19.6%)	15 (20.8%)	0.81	0.32–2.03		

Multivariable analysis includes age, ASA grade, pancreatic resection, type of tumor, and pNET ≥2 cm. Missing data were observed for size pNET imaging (6.5%), pNET size ≥ 2 cm (6.5%), suspected lymph node metastases on imaging (0.8%), and suspected liver metastases on imaging (0.8%). For all other variables no missing data were observed.
ASA, American Society of Anesthesiologists; *CI*, confidence interval; *F-pNET*, functioning pancreatic neuroendocrine tumor; *NF-pNET*, non-functioning pancreatic neuroendocrine tumor; *No*, number of; *OR*, odds ratio; *Ref*, reference category.
* Data given after multiple imputation.
† For comparison between patients with and without a severe complication median (range) is presented.

Table II
Baseline characteristics

Characteristic	Overall N = 123
Age at surgery in years, mean (SD)	54 (±14)
Sex, n (%)	
Male	59 (48.0%)
Female	64 (52.0%)
Surgical indication, n (%)	
NF-pNET	87 (70.7%)
Insulinoma	26 (21.1%)
Gastrinoma	2 (1.6%)
Glucagonoma	1 (0.8%)
Somatostatinoma	1 (0.8%)
NF-pNET and gastrinoma	6 (4.9%)
Hereditary syndrome, n (%)	
MEN1	22 (17.9%)
von Hippel-Lindau	5 (4.1%)
ASA grade, n (%)	
1	25 (20.3%)
2	75 (61.0%)
3	22 (17.9%)
4	1 (0.8%)
Preoperative imaging performed, n (%)	
Magnetic resonance imaging	53 (43.1%)
Computed tomography	110 (89.4%)
Endoscopic ultrasonography	82 (66.7%)
Somatostatin receptor scintigraphy	28 (22.8%)
^{68}Gallium labelled PET/CT	65 (52.8%)
^{68}Ga-DOTATATE PET/CT	28 (22.8%)
^{68}Ga-DOTATOC PET/CT	8 (6.5%)
^{68}Ga-DOTANOC PET/CT	1 (0.8%)
^{18}F-DOPA PET/CT	15 (12.2%)
^{18}F-FDG PET/CT	1 (0.8%)
^{11}C-5-HTP PET	12 (9.8%)
pNETs on preoperative imaging (n = 122 [99.2%]), n (%)	
Solitary	91 (74.6%)
Multiple	31 (25.4%)
Preoperative tumor localization, n (%)	
Head	59 (48.0%)
Body	9 (7.3%)
Tail	48 (39.0%)
Multifocal	7 (5.7%)
Size largest pNET on conventional imaging in mm (n =115 [93.5%]), median (range)	23 (6 - 140)
pNET ≥2 cm on preoperative imaging (n = 115 [93.5%]), n (%)	71 (61.7%)
Suspected lymph node metastases on imaging (n = 122 [99.2%]), n (%)	30 (24.6%)
Suspected liver metastases on imaging (n = 122 [99.2%]), n (%)	22 (17.9%)
Procedures, n (%)	
Enucleation	12 (9.8%)
Distal pancreatectomy	50 (40.7%)
PPPD/Whipple	51 (41.5%)
Total pancreatectomy	6 (4.9%)
Combined resection	4 (3.3%)
Approach, n (%)	
Conventional/open	82 (66.7%)
Laparoscopic	16 (13.0%)
Robot-assisted	25 (20.3%)
Additional resection for suspected pNET metastases, n (%)	7 (7.3%)

ASA, American Society of Anesthesiologists; *MEN1*, multiple endocrine neoplasia type 1; N number of; *NF-pNET*, non-functioning pancreatic neuroendocrine tumor; *PET*, positron emission tomography; *pNET*, pancreatic neuroendocrine tumor; *PPPD*, pylorus-preserving pancreatoduodenectomy; *SD*, standard deviation.

within the family. Patients with MEN1/VHL were younger at surgery, more often had multiple pNETs on imaging, and more frequently underwent a total/combined pancreatectomy as compared to patients with sporadic disease (Table III). The median age at surgery in patients with MEN1 and in patients with VHL was 41.5 years (6–62) and 42.0 years (33–51), respectively. Overall, the majority of patients had an NF-pNET (70.7%). Preoperatively, NF-pNETs were generally larger than F-pNETs, and more NF-pNETs were ≥2 cm (72.3 vs 34.3%; Table III). Three patients had prior resection of a pNET.

Surgical procedures

The majority of patients ($n = 51$; 41.5%) underwent a Whipple procedure ($n = 9$) or PPPD ($n = 42$). Fifty patients (40.7%) underwent a DP, of whom 27 (54.0%) had a spleen-preserving procedure; spleen-preserving DP was more often performed robot-assisted, and tumors were generally smaller (Supplementary Table S1). In 21 patients, splenectomy was planned due to preoperative or intraoperative suspicion of either direct tumor involvement or close relation with the spleen or splenic vessels. In the remaining 2, splenectomy was performed owing to intraoperative iatrogenic damage to the splenic vessels. Enucleation was performed in 12 patients (9.8%)—5 tumors were located in the pancreatic head and 7 in the body or tail. In 10 of these, the distance to the main pancreatic duct was determined by intraoperative ultrasound. In 7 patients in the enucleation group, no anastomosis was constructed. A Roux-en-Y reconstruction was performed in 3 patients, of whom 1 also had a serosal patch. Six patients (4.9%) underwent a total pancreatectomy—2 were duodenum-preserving. Four patients (3.3%) underwent a combined resection; these were exclusively performed in patients with MEN1 and multifocal disease and included a Whipple/PPPD plus DP in 3 and an enucleation plus DP in 1. Synchronous hepatic resections for pNET-related metastases were performed in 6 patients (4.9%), and 1 patient underwent synchronous resections of metastases in the stomach and kidney. Liver resections included hemihepatectomy ($n = 2$), right hemihepatectomy plus wedge resection ($n = 1$), wedge resection plus radiofrequency ablation ($n = 1$), multiple wedge resections ($n = 1$), and segmentectomies ($n = 1$). Two patients underwent multivisceral resections due to tumor progression, and 4 other patients underwent synchronous resections due to compromise of the colonic ($n = 1$) or omental vasculature ($n = 1$), gastric NET ($n = 1$), or renal cell carcinoma ($n = 1$). Forty-one of the procedures (33.3%) were minimally invasive, of which 3 were converted.

Intraoperative and postoperative complications

The median durations of surgery and blood loss were 309 minutes (76–1,062) and 450 milliliters (0–5,000), respectively. A relaparotomy was performed in 8 patients (6.5%)—indications were POPF in 3 patients (all grade C), PPH in 2 (grade B and C), bile leak in 1 (grade C), and fascial dehiscence in 1. The remaining patient underwent 3 relaparotomies for omental necrosis, POPF grade C, and abdominal abscesses, respectively. The median LOS was 11 days (4–260).

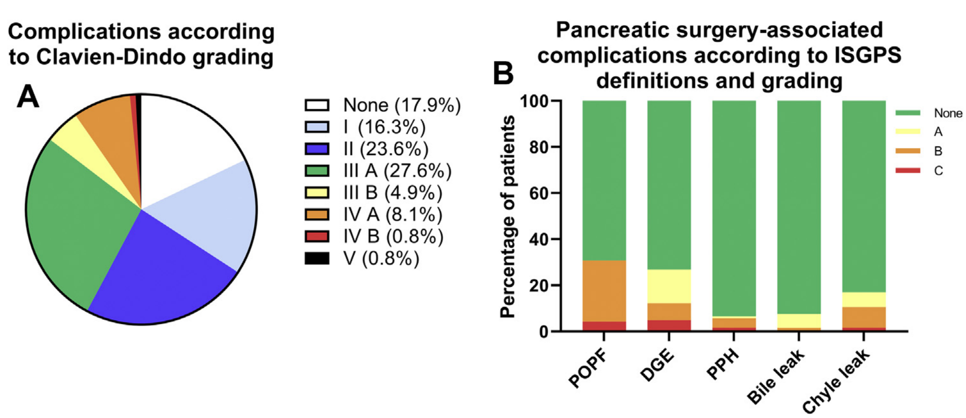
A severe complication was observed in 51 patients (41.5%) (Figure 1); 13 of these had a grade 3 complication due to endoscopic feeding tube placement. The only death (0.8%) within 90 days occurred in a patient that suffered from a perioperative stroke with a fatal prognosis. The overall failure-to-rescue rate was 2.0% ($n = 1/51$) and for ISGPS grade B/C complications 0% ($n = 0/51$). Patients with a severe complication had a longer LOS (20 [6–260] vs 8 [4–30] days; $P < .001$) than patients with no severe complication. The median CCI was 22.6 (0–100), leading to associated estimated costs of €15,336 (€10,098–€46,402) and $45,775 ($30,140–$138,497), respectively. Twenty-nine patients (23.6%) of patients had a high CCI.

Procedure-related outcomes are presented in Table IV. The risk for a severe complication, a cumulative CCI ≥37.1, and any grade B/C complication and the cumulative CCI as well as the number of complications were procedure-related (Table IV; Figure 2). A POPF

Table III
Characteristics and outcomes of patients with a MEN1/VHL-related versus sporadic pNET and F-pNET versus NF-pNET

Characteristic	Sporadic n = 96	MEN1/VHL n = 27	P value	NF-pNET n = 87	F-pNET n = 36	P value
Age at surgery in years, median (range)	57 (21–81)	42 (6–62)	<.001	56 (19–79)	53 (6–81)	.178
Sex						
Male	46 (47.9%)	13 (48.1%)	.983	46 (52.9%)	13 (36.1%)	.090
Female	50 (52.1%)	14 (51.9%)		41 (47.1%)	23 (63.9%)	
Hereditary syndrome						
MEN1	NA	NA	NA	12 (13.8%)	10 (27.8%)	.079
von Hippel-Lindau				5 (5.7%)	0 (0%)	
Type of pNET						
NF-pNET	70 (72.9%)	17 (63.0%)	.315	NA	NA	NA
F-pNET	26 (27.1%)	10 (37.0%)				
ASA grade						
1	21 (21.9%)	4 (14.8%)	.804	19 (22.8%)	6 (16.7%)	.523
2	57 (59.4%)	18 (66.7%)		54 (62.1%)	21 (58.3%)	
3	17 (17.7%)	5 (18.5%)		13 (14.9%)	9 (25.0%)	
4	1 (1.0%)	0 (0%)		1 (1.1%)	0 (0%)	
Number of pNETs imaging, n = 122 (99.2%)						
Solitary	83 (87.4%)	8 (29.6%)	<.001	65 (74.7%)	24 (66.7%)	.364
Multiple	12 (12.6%)	19 (70.4)		22 (25.3%)	12 (33.3%)	
Size largest pNET on conventional imaging in mm, median (range), n = 115 (93.5%)	22 (6–140)	24 (8–98)	.781	27 (8–120)	15 (6–140)	<.001
pNET ≥ 2 cm on preoperative imaging, n = 115 (93.5%)	52 (58.4%)	19 (73.1%)	.176	60 (72.3%)	11 (34.4%)	<.001
Suspected lymph node metastases on imaging, n = 122 (99.2%)	21 (22.1%)	9 (33.3%)	.232	23 (26.7%)	7 (19.4%)	.393
Suspected liver metastases on imaging, n = 122 (99.2%)	17 (17.9%)	5 (18.5%)	.941	17(19.8%)	5 (13.9%)	.441
Procedures			<.001			.185
Enucleation	10 (10.4%)	2 (7.4%)		7 (8.0%)	5 (13.9%)	
Distal pancreatectomy	41 (42.7%)	9 (33.3%)		32 (36.8%)	18 (50.0%)	
PPPD/whipple	43 (44.8%)	8 (29.6%)		42 (48.3%)	9 (25.0%)	
Total pancreatectomy	2 (2.1%)	4 (14.8%)		4 (4.6%)	2 (5.6%)	
Combined resection	0 (0%)	4 (14.8%)		2 (2.3%)	2 (5.6%)	
Approach			.714			.654
Open	63 (65.6%)	19 (70.4%)		60 (69.0%)	22 (61.1%)	
Laparoscopic	12 (12.5%)	4 (14.8%)		10 (11.5%)	6 (16.7%)	
Robot-assisted	21 (21.9%)	4 (14.8%)		17 (19.5%)	8 (22.2%)	

Patients with both a NF-pNET and gastrinoma were analyzed as F-pNET.
ASA, American Society of Anesthesiologists; *DGE*, delayed gastric emptying; *F-pNET*, functioning pancreatic neuroendocrine tumor; *MEN1*, multiple endocrine neoplasia type 1; *N*, number of; *NF-pNET*, non-functioning pancreatic neuroendocrine tumor; *pNET*, pancreatic neuroendocrine tumor; *POPF*, postoperative pancreatic fistula; *PPH*, post-pancreatectomy hemorrhage; *PPPD*, pylorus-preserving pancreatoduodenectomy.



	POPF	DGE	PPH	Bile leak	Chyle leak
A	-	18 (14.6%)	1 (0.8%)	4 (6.1%)	8 (6.5%)
B	32 (27.4%)	9 (7.3%)	5 (4.1%)	1 (1.5%)	11 (8.9%)
C	4 (3.4%)	6 (4.9%)	2 (1.6%)	1 (1.5%)	2 (1.6%)

Figure 1. Postoperative complications. (A) Pie-chart showing the percentage of patients with complications according to the Clavien-Dindo classification. (B) Bar graphs showing the percentage of patients with pancreatic surgery-associated complications according to the ISGPS definitions and grading. For the bile leak analysis, only patients with resections of the pancreatic head were included, that is, patients after a Whipple/pylorus-preserving pancreatoduodenectomy, total pancreatectomy, combined pancreatectomy, and enucleation of the pancreatic head. *DGE,* delayed gastric emptying; *ISGPS,* International Study Group of Pancreatic Surgery; *POPF,* postoperative pancreatic fistula; *PPH,* post-pancreatectomy hemorrhage.

Table IV
Procedure-specific intraoperative outcomes and postoperative complications

	Enucleation (n = 12)	Distal pancreatectomy (n = 50)	PPPD/ Whipple (n = 51)	Total or combined pancreatectomy (n = 10)	P value
Intraoperative outcomes					
Duration of surgery in minutes, n = 122 (99.2%)	224 (76–485)	254 (115–582)	378 (166–810)	359 (289–1,089)	<.001
Blood loss in mL, n = 117 (95.1%)	125 (0–1,000)	400 (0–5,000)	600 (150–4,500)	775 (200–2,000)	<.001
Hospital stay					
Length of stay in days, n = 117 (95.1%)	7 (4–12)	8 (4–64)	15 (7–51)	23 (7–260)	<.001
Re-laparotomy	0 (0%)	3 (5.9%)	3 (5.9%)	2 (20.0%)	.274
ICU admission	0 (0%)	2 (4.0%)	7 (13.7%)	3 (30.0%)	.033
Postoperative complications					
Number of complications	1 (0–5)	1 (0–10)	2 (0–12)	4 (0–17)	.001
Clavien-Dindo grade					–
None	4 (33.3%)	14 (28.0%)	3 (5.9%)	1 (10.0%)	
I	3 (25.0%)	9 (18.0%)	6 (11.8%)	2 (20.0%)	
II	4 (33.3%)	10 (20.0%)	13 (25.5%)	2 (20.0%)	
III A	1 (8.3%)	12 (24.0%)	19 (37.3%)	2 (20.0%)	
III B	0 (0%)	3 (6.0%)	3 (5.9%)	0 (0%)	
IV A	0 (0%)	2 (4.0%)	6 (11.8%)	2 (20.0%)	
IV B	0 (0%)	0 (0%)	0 (0%)	1 (10.0%)	
V	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)	
Clavien-Dindo ≥III	1 (8.3%)	16 (32.0%)	29 (56.9%)	5 (50.0%)	.006
CCI	12.25 (0–33.17)	20.92 (0–92.94)	29.58 (0–100)	32.12 (0–100)	<.001
CCI ≥37.1	0 (0%)	6 (12.0%)	18 (35.3%)	5 (50.0%)	.002
Pancreatic surgery specific complications					
POPF B/C	0 (0%)	16 (32.0%)	18 (35.3%)	2 (50.0%)*	.088
DGE B/C	0 (0%)	1 (2.0%)	11 (21.6%)	3 (75.0%)	.003
PPH B/C	0 (0%)	2 (4.0%)	1 (2.0%)	4 (40.0%)†	<.001
Bile leak B/C‡	0 (0%)	NA	2 (4.0%)	0 (0%)	.800
Chyle leak B/C	0 (0%)	5 (10.0%)	8 (15.7%)	0 (0%)	.258
Any B/C complication	0 (0%)	19 (38.0%)	26 (51.0%)	6 (60.0%)	.007
Estimated associated costs					
Euro, €	12,444 (11,400–17,292)	14,577 (10,098–42,035)	16,442 (10,098–46,402)	17,695 (10,098–46,402)	<.001
USD, $	37,143 (34,025–51,611)	43,507 (30,140–125,463)	49,300 (30,140–138,497)	52,817 (30,140–138,497)	<.001

Continuous variables reported as median (range).
CCI, comprehensive complication index; *DGE*, delayed gastric emptying; *ICU*, intensive care unit; *POPF*, postoperative pancreatic fistula; *PPH*, post-pancreatectomy hemorrhage; *PPPD*, pylorus-preserving pancreatoduodenectomy; *USD*, United States dollar.
* For the POPF analysis, patients with a total pancreatectomy were removed from the denominator.
† Two of the 6 patients after a total pancreatectomy and 2 of the 4 patients after a combined resection developed a PPH.
‡ For the bile leak B/C analysis, only patients with surgery of the pancreatic head were included, ie, patients after a Whipple/PPPD, total pancreatectomy and enucleation of the pancreatic head.

grade B/C was the most frequently occurring pancreas surgery-specific complication (n = 36 [29.3%]). After an enucleation, none of the patients developed any ISGPS grade B/C complication. Delayed gastric emptying was significantly more often observed after a Whipple/PPPD or total/combined pancreatectomy. In addition, a grade B/C PPH occurred more often after a total/combined pancreatectomy. One of the 2 patients with a combined pancreatectomy suffered from POPF and the other from multiple abscesses and a pseudoaneurysm of the superior mesenteric artery. In the total pancreatectomy group, 1 patient suffered from intraluminal jejunal bleeding and 1 patient from bleeding in the retroperitoneal dissection area.

Factors associated with a severe complication and grade B/C POPF

A severe complication was observed more often in male patients versus female patients, in patients with a MEN1/VHL-related pNET versus sporadic pNET, and in patients with an ASA grade of 3/4 vs 1/2, respectively. Besides procedure type, no characteristics were significantly associated with the occurrence of a severe complication in univariable analysis (Table I). After adjusting for age at surgery, ASA grade, type of pNET, and presence of a pNET ≥2 cm, patients in the Whipple/PPPD group had an increased risk for a severe complication compared to those in the DP group (OR 3.13 [95% CI 1.32–7.41]; Table I). Sensitivity analyses did not substantially influence the effect size (point estimate or 95% CI; Supplementary Table S2). No factors were associated with a POPF grade B/C (Supplementary Table S3).

MEN1/VHL versus sporadic pNET

In terms of percentage, patients with MEN1/VHL more often had a severe complication, POPF, any grade B/C complication, and a cumulative CCI ≥37.1; DGE, and PPH occurred significantly more often (Table V). After minor resections, complication percentages were similar. In the major resection group, a severe complication and ISGPS grade B/C POPF, DGE, PPH occurred more often in patients with MEN1/VHL. The number of complications and the CCI was significantly higher in patients with MEN1/VHL as compared to sporadic disease after major resections (45.1 vs 28.9, P = .029). In addition, the percentage of patients with a cumulative CCI ≥37.1 was higher in MEN1/VHL-related pNETs as compared to those with sporadic pNETs.

Of the patients with MEN1/VHL and a major resection, 68.8% (n=11/16) developed a severe complication compared to 27.3% (n=3/11) after a minor resection. Within the subgroups of patients with sporadic and MEN1/VHL-related pNETs, the CCI was significantly higher after major resections (sporadic 28.9 versus 12.2, p=0.001 and MEN1/VHL 45.1 versus 20.9, p=0.005, respectively). In patients with a resected sporadic pNET a severe complication occurred significantly more often after major resections (51.1% versus 27.5%, p=0.017).

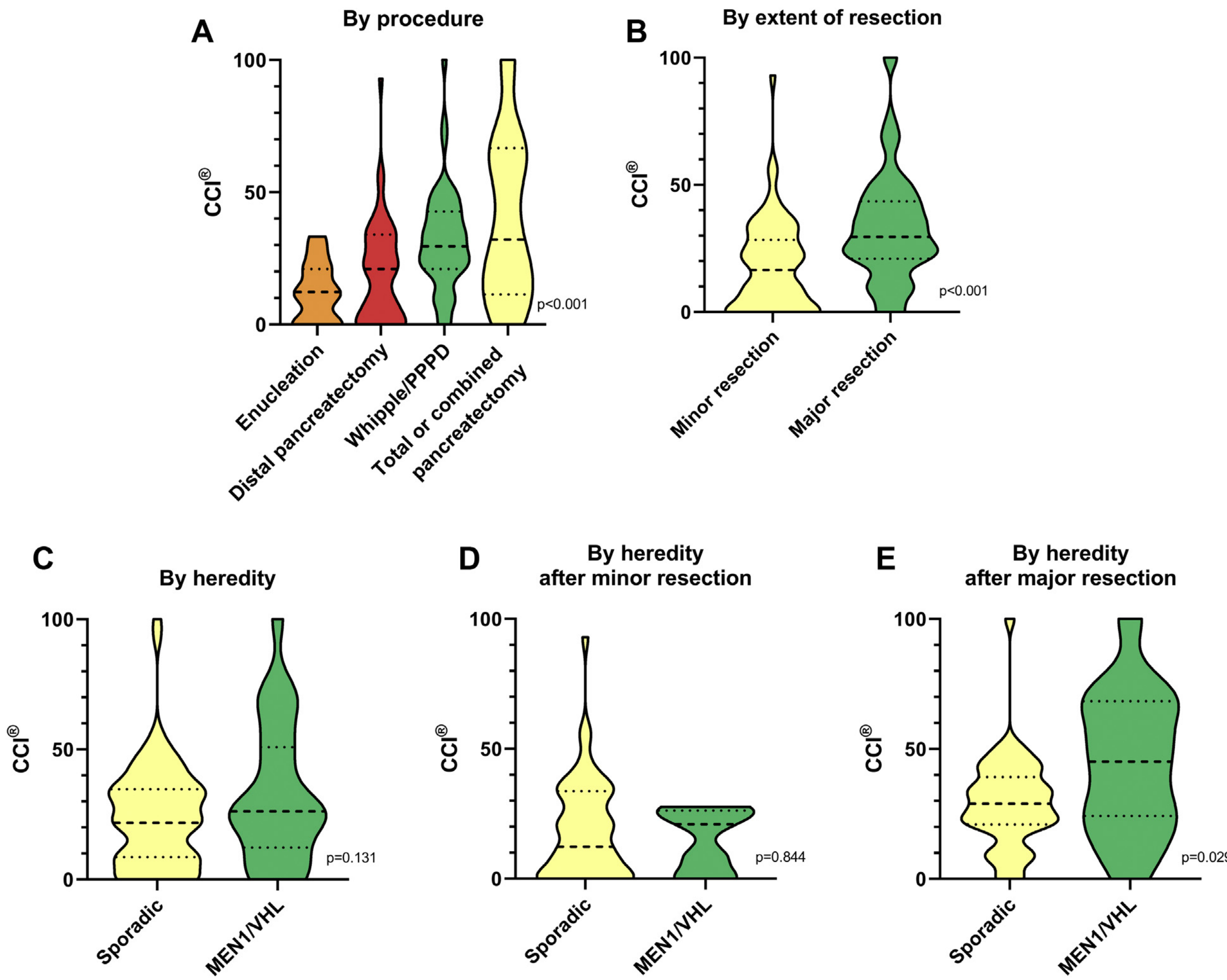


Figure 2. Violin plots showing the distribution of the CCI. (A) By surgical procedure. (B) By extent of resection. (C) By hereditary syndrome. (D) By heredity. (E) By heredity after minor resection. *CCI,* comprehensive complication index; *MEN1,* multiple endocrine neoplasia type 1; *pNET,* pancreatic neuroendocrine tumors; *PPPD,* pylorus-preserving pancreatoduodenectomy; *VHL,* von Hippel-Lindau.

F-pNET versus NF-pNET

The occurrence of complications between patients with an F-pNET as compared to those with an NF-pNET are presented in Supplementary Table S4. Overall occurrence of complications and pancreatic surgery-associated complications was similar between both groups. In the group undergoing minor resections, no differences were observed, whereas after major resections, the CCI was higher in the F-pNET group (37.1 vs 27.6, $P = .031$). Patients with functioning pNETs more often underwent total or combined resections (30.8% vs 12.5%) and had MEN1/VHL (46.2% vs 20.8%), which likely contributed to the observed differences. No differences were observed in metastatic status. For both the F-pNET and NF-pNET subgroups, patients undergoing major resections had a significantly higher risk for a severe complication, DGE and cumulative CCI ≥37.1, and a higher number of complications, CCI, and estimated costs.

No differences in complications were observed between patients with a radiological NF-pNET of <2 or ≥2 cm. However, in patients with an NF-pNET <2 cm, those undergoing major resections suffered significantly more often from a severe complication, any grade B/C complication, and had a higher CCI (Supplementary Table S5).

Discussion

This study investigated the incidence and severity of complications and risk factors for complications after resections of pNETs in 2 ENETS Centers of Excellence. Although mortality was low (0.8%), a severe complication occurred in 41.5% of patients. An increased risk for a severe complication, independent of age, ASA grade, tumor functionality, and a radiological pNET of 2.0 cm or more, was observed in patients undergoing a Whipple/PPPD versus those undergoing a DP. A higher percentage of patients with MEN1/VHL—especially those undergoing major resections—had complications than those with sporadic disease, and the cumulative burden of complications was higher.

A meta-analysis reported mortality rates after operations for pNETs as high as 3% to 6%, depending on the procedure performed.[22] In contrast, mortality was 0.8% (procedure-specific range 0% to 2%) in the present study, which is similar to several more recent cohort studies within expert centers reporting mortality rates between 0% and 1.5%.[14–19,41] This most likely reflects improved outcomes after centralization of pNET care and pancreatic surgery.[24] The rate of complications was substantial, but only 2% of patients with a severe complication died, indicating that the failure-to-rescue was low. Moreover, no patient died of a grade B/C

Table V
Complications according to extent of resections and presence of MEN1/VHL

Characteristic	Overall			Minor resection			Major resection		
	Sporadic n = 96	MEN1/VHL n = 27	P value	Sporadic n = 51	MEN1/VHL n = 11	P value	Sporadic n = 45	MEN1/VHL n = 16	P value
Clavien-Dindo ≥III, n (%)	37 (38.5%)	14 (51.9%)	.215	14 (27.5%)	3 (27.3%)	1.000	23 (51.1%)	11 (68.8%)	.222
POPF B/C, n (%)*	27 (28.7%)	9 (39.1%)	.332	13 (25.5%)	3 (27.3%)	1.000	14 (32.6%)	6 (50.0%)	.267
DGE B/C, n (%)	8 (8.3%)	7 (25.9%)	.014	1 (2.0%)	0 (0%)	1.000	7 (15.6%)	7 (50.0%)	.021
PPH B/C, n (%)	3 (3.1%)	4 (14.8%)	.041	2 (3.9%)	0 (0%)	1.000	1 (2.2%)	4 (25.0%)	.015
Bile leak B/C, n (%)†	1 (2.1%)	1 (5.6%)	.464	0 (0%)	0 (0%)	1.000	1 (2.2%)	1 (6.3%)	.459
Chyle leak B/C, n (%)	11 (11.5%)	2 (7.4%)	.731	4 (7.8%)	1 (9.1%)	1.000	7 (15.6%)	1 (6.3%)	.668
Any B/C, n (%)	36 (37.5%)	15 (55.6%)	.092	15 (29.4%)	4 (36.4%)	.724	21 (46.7%)	11 (68.8%)	.129
CCI	20.92 (0–100)	26.22 (0–100)	.131	12.25 (0–92.94)	20.92 (0–27.61)	.844	28.94 (0–100)	45.12 (0–100)	.029
CCI ≥37.1, n (%)	19 (19.8%)	10 (37.0%)	.062	6 (11.8%)	0 (0%)	.580	13 (28.9%)	10 (62.5%)	.017
Number of complications	1 (0–10)	2 (0–17)	.034	1 (0–10)	1 (0–2)	.618	2 (0–6)	4.5 (0–17)	.001
Euro, €	15,336 (10,094–6,402)	14,683 (10,094–6,402)	.864	14,564 (10,098–42,035)	13,534 (10,098–15,710)	.160	16,400 (10,098–46,402)	19,953 (10,098–46,402)	.176
USD, $	45,775 (30,140–138,497)	44,362 (30,140–138,497)	0.924	43,471 (30,140–125,463)	40,396 (30,140–46,890)	0.144	49,074 (30,140–138,497)	59,556 (30,140–138,497)	.187

Continuous variables presented as median (range). Minor resections include enucleations and distal pancreatectomies. Major resections include Whipple/PPPDs, total pancreatectomies, and combined resections.
CCI, comprehensive complication index; *DGE*, delayed gastric emptying; *N*, number of; *POPF*, postoperative pancreatic fistula; *PPH*, post-pancreatectomy hemorrhage; *USD*, United States dollars.
* For the POPF analysis, patients with a total pancreatectomy were removed from the denominator.
† For the bile leak B/C analysis, only patients with surgery of the pancreatic head were included, ie, patients after a Whipple/PPPD, total pancreatectomy, combined pancreatectomy, and enucleation of the pancreatic head.

pancreatic surgery-associated complication. This is in line with observations in the Netherlands that the failure-to-rescue is generally lower in high-volume than in low-volume centers.[42] Mortality and failure-to-rescue rates were below benchmark cutoffs—established within low-risk pancreatoduodenectomy cases in 23 international high-volume centers in pancreatic surgery—-whereas the CCI and severe complications fell within the 75th percentile.[43] Over the years, a nationwide collaboration has been established to improve outcomes after pancreatic surgery. Although their results and experience likely have improved surgical outcomes, ongoing prospective studies—which predominantly included patients after the present study—will evaluate whether nationwide standardization of postoperative care will decrease the rates of major morbidity and POPF.

Rates of a severe complication ranged from 15.0% to 30.7% in other series, which is lower than in the present data.[14,19,41] Complications were the primary outcome of the present study and were therefore precisely assessed and graded according to the Clavien-Dindo and ISGPS criteria and definitions. In addition, the present study included a high number of major pancreatectomies—49.6% of the current cohort—compared to 21.3% to 31.7% in these other studies.[14,19,41] The risk of complications was procedure-specific, as severe morbidity was observed in more than half of the Whipple/PPPD cases. Overall, endoscopic feeding tube placement for DGE contributed to the incidence of severe morbidity, as 13 patients had a single Clavien-Dindo grade 3 complication due to endoscopic feeding tube placement for DGE.

The overall rate of POPF grade B/C is considerably higher than the 12% to 13% after ‘general’ pancreatic operations.[44] Patients with a pNET generally have a soft pancreas, which induces a higher exocrine activity with more enzyme-rich pancreatic fluid, a main pancreatic duct of less than 3 mm, more side branches, and a reduced suture holding capacity, which complicate the operation.[12,13,45] In this respect, others have shown that pancreatoduodenectomy for pNET as compared with adenocarcinoma is associated with POPF.[13] In that study, 82% of patients with pNETs had a soft pancreas, and the median main pancreatic duct size was 3 mm.[13] The combination of soft texture and a main pancreatic duct diameter ≤3 mm gives the highest risk of POPF after pancreatoduodenectomy.[46] Nevertheless, the POPF rate in the present study was 30.8%, which compares favorably to the 34.3% observed after surgical resection for pNETs in another high-volume expert center adopting the 2016 ISGPS criteria.[23] Intervention-driven complication classification systems, such as the Clavien-Dindo and ISGPS definitions, lead to high percentages of complications, whereas early identification and timely treatment, such as percutaneous drainage for POPF, are aimed at reducing the incidence of multiorgan failure and mortality.

In contrast to several other studies comparing complications after resections for pNETs, which have reported a higher rate of POPF in patients undergoing a pancreas-sparing operation (ie, enucleation) versus a standard resection (ie, DP or pancreatoduodenectomy), none of the patients in the enucleation group suffered from a POPF.[16,19,22,23] Potential explanations include the low number of patients undergoing an enucleation, improved patient selection—in most patients, intraoperative ultrasound was used to determine the distance to the main pancreatic duct—and expertise in surgical teams in the present series. Although a meta-analysis observed a higher rate of POPF after enucleations compared to standard resections, this risk was not increased in high-volume centers.[47] Only 1 patient developed a severe complication in the present series, indicating that enucleation may be superior regarding complications in selected patients. The feasibility of enucleation depends on tumor location, size, and distance from the main pancreatic duct.[48]

In the context of complications, little is known about patients with MEN1/VHL versus sporadic disease. Patients with MEN1 are generally affected by multifocal pNETs and even duodenal tumors, whereas patients with VHL usually have cystic pancreatic tissue, making surgery more difficult. In the present study, a severe complication, POPF, DGE and PPH, occurred more often in patients with a MEN1/VHL. A previous study observed POPF more often in patients with hereditary pNETs and those with combined resections.[18] The stratified analysis demonstrated that the risk of complications was similar between both groups after minor resections. In contrast, after major resections, patients with a MEN1/VHL-related syndrome had a 17.5% higher risk of a severe complication, and the percentage of PPH and DGE and the cumulative burden of complications were significantly higher. This extremely high-risk—2 out of 3 patients developed a severe complication—can be attributed to the high proportion of total and combined pancreatectomies, which were almost exclusively performed in patients with multifocal pNETs. The combined resections have only rarely been described.[21,48,49] Along with the risks of a soft pancreas, patients undergoing a Whipple/PPPD plus DP are more prone to leakage from the pancreatic anastomosis as well as stump leakage from the cutting surface. This severe morbidity underscores the importance of adequate risk stratification and centralization of patients with MEN1/VHL-related pNETs—which are substantially younger and affected by multifocal disease—in multidisciplinary tumor boards and surgical teams with vast experience in pNETs and MEN1/VHL.

Performing surgery for pNETs is a risk–benefit balance between the oncological benefit versus the risk of complications. The complication rate and morbidity are high. Nevertheless, the latter does not mean that these operations should not be performed since surgeons have an excellent rate of rescue from complications and these tumors can be malignant. Within the present study, no disease-related factors, such as tumor size, were identified that were related to the occurrence of complications and could subsequently contribute to patient selection. The extent of surgery was the most important predictor for severe complications. These data are relevant to guide preoperative patient counseling and enable shared decision-making regarding the timing and the extent of resection.

The observed complication and failure-to-rescue rates were observed in 2 ENETS Centers of Excellence. Therefore, these results might not necessarily be applicable to lower-volume hospitals. Although no comparison was made with lower-volume hospitals, these data imply that surgery for pNETs should be reserved for centers of excellence. First, as shown, within these centers, the failure-to-rescue rate is low, likely due to timely detection of complications on the wards and adequate management of these patients by surgeons, gastroenterologists, or interventional radiologists. Second, surgeons should be familiar with all (unconventional) pancreatic procedures, as these might provide excellent oncologic outcomes, and the risk of complications is procedure-specific. Third, centers of excellence often have a dedicated multidisciplinary team that enables adequate preoperative risk stratification. Fourth, patients with hereditary syndromes often undergo extensive procedures, such as combined pancreatectomies, which are associated with a high risk of complications, therefore underscoring the importance of adequate risk stratification of each tumor in these patients.

The major strength of the present study is the comprehensive, sequential cohort of patients, including both sporadic- and MEN1/VHL-related pNETs, from 2 expert centers, including results from many surgeons operating patients with pNETs over a recent period, thereby accurately reflecting current day practice. Large administrative databases are often not specific enough to provide a detailed assessment of postoperative complications. The recent study period assured electronic patient records with extensive information, including postoperative notes, discharge letters, imaging reports, laboratory values, and reinterventions, thereby ensuring complete and reliable assessment of every individual patient's postoperative course. To accurately capture and grade every complication demands substantial effort, which is a specific strength of this study. Complications were systematically assessed and graded according to the most recent accepted and validated classifications.[29,32,50] Missing data were encountered and imputed using multiple imputation, which currently is the best statistical method to handle missing data.[51] The main limitation includes the relatively small sample size, which limited covariate adjustment. In addition, pancreatic texture and pancreatic duct size, known risk factors for POPF after pancreatoduodenectomy, were not available for analysis and could not be retrieved given the retrospective study design. The number of patients in the enucleation group was limited, and, therefore, enucleations of the head and those of the body/tail were grouped. Ideally, enucleations would be the reference group for multivariable analysis, but this was impossible considering the low number of complications. Estimated costs were only estimated by methods proposed by Staiger et al[30] and not directly calculated by combining all costs associated with the operation and subsequent postoperative care.

This study shows that resections for pNETs can be safely performed in ENETS Centers of Excellence. Although a considerable and procedure-dependent risk of severe morbidity was observed, mortality and failure-to-rescue were low. These data will aid preoperative patient counseling and might additionally be used for shared decision-making regarding the timing and the extent of surgical resection. Patients with MEN1/VHL-related pNETs are a challenging surgical entity and therefore warrant specialized care.

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Conflict of interest/Disclosure

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2022.02.007].

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