Published in final edited form as:
World J Surg. 2012 July ; 36(7): 1517–1526. doi:10.1007/s00268-012-1598-9.

Rate of Clinically Significant Postoperative Pancreatic Fistula in Pancreatic Neuroendocrine Tumors

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Abstract

Background—In 2005, the International Study Group of Pancreatic Fistula (ISGPF) developed a definition and grading system for postoperative pancreatic fistula (POPF). The authors sought to determine the rate of POPF after enucleation and/or resection of pancreatic neuroendocrine tumors (PNET) and to identify clinical, surgical, or pathologic factors associated with POPF.

Methods—A retrospective analysis of pancreatic enucleations and resections performed from March 1998 to April 2010. We defined a clinically significant POPF as a grade B that required nonoperative intervention and grade C.

Results—One hundred twenty-two patients were identified; 62 patients had enucleations and 60 patients had resections of PNET. The rate of clinically significant POPF was 23.7 % (29/122). For

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pancreatic enucleation, the POPF rate was 27.4 % (17/62, 14 grade B, 3 grade C). The pancreatic resection group had a POPF rate of 20 % (12/60, 10 grade B, 2 grade C). This difference was not significant ($p = 0.4$). In univariate analyses, patients in the enucleation group with hereditary syndromes ($p = 0.02$) and non-insulinoma tumors ($p = 0.02$) had a higher POPF rate. Patients in the resection group with body mass index (BMI) >25 ($p < 0.01$), multiple endocrine neoplasia type 1 (MEN-1; $p < 0.01$) and those who underwent simultaneous multiple procedures ($p = 0.02$) had a higher POPF rate. Multivariate analyses revealed that hereditary syndromes were able to predict POPF in the enucleation group, while having BMI >25 and increasing lesion size were also associated with POPF in the group undergoing resection.

Conclusions—We found a clinically significant POPF rate after surgery in PNET to be 23.7 % with no difference by the type of operation. Our POPF rate is comparable to that reported in the literature for pancreatic resection for other types of tumors. Certain inherited genetic diseases—von Hippel–Lindau disease (VHL) and MEN-1—were associated with higher POPF rates.

Introduction

Postoperative pancreatic fistula (POPF) is a well-described complication after pancreatic surgery; it is associated with significant morbidity and occurs in up to 50 % of patients [1–7]. Prior to the recent establishment of a universal definition, it was difficult to compare POPF rates published in the literature. In 2005, the International Study Group of Pancreatic Fistula (ISGPF) developed a universal objective definition and grading system for the severity of POPF [3]. A uniform definition provides an opportunity to accurately compare POPF rates among different institutions, surgical techniques, surgical procedures, histologies, and clinical factors. Since the ISGPF definition has been established, most of the published data for POPF focuses on pancreatic resection for pancreatic adenocarcinoma with little focus on pancreatic neuroendocrine tumors (PNET) or pancreatic enucleation. The rates of POPF, using the ISGPF criteria, range from 17 to 39 % [8–12].

Pancreatic neuroendocrine tumors are rare, representing only 1–2 % of all pancreatic neoplastic lesions [13]. The incidence of PNET is approximately 1 per 100,000 persons per year in the general population [13, 14]. Pancreatic neuroendocrine tumors arise from endocrine pancreatic cells or the islets of Langerhans, unlike pancreatic adenocarcinomas, which make up >95 % of pancreatic tumors and arise from the exocrine or ductal cells of the pancreas [15–17]. Pancreatic neuroendocrine tumors are usually well-differentiated, slow growing, and, if malignant, carry a better prognosis than pancreatic adenocarcinomas [14]. The majority of PNET are sporadic; however about 10–15 % are associated with inherited genetic diseases such as MEN-1, VHL, neurofibromatosis (NF), and tuberous sclerosis (TSC) [18]. Up to 17 % of VHL patients [19, 20] and up to 55.4 % of MEN-1 patients will develop a PNET [21].

Surgery is the cornerstone of therapy for patients with PNET. Surgery is the only potentially curative treatment available and is indicated for patients with a PNET to control hormone hypersecretion, local compressive symptoms, malignancy, and for palliation of symptoms in patients with advanced disease. Parenchymal sparing techniques such as pancreatic enucleation as well as the utilization of laparoscopic technology have shown similar long-term survival compared to resection and laparotomy in patients with PNET [22]. Pancreatic enucleation of small local PNET has been the surgical paradigm. Limited data have been published evaluating the impact of surgical technique on the development of POPF in PNET.

The purpose of the present study was to determine the rate of clinically significant POPF for PNET and to evaluate if a difference exists in POPF rate by surgical technique—pancreatic enucleation versus resection. The study also sought to identify any clinical, surgical, or

pathologic factors that may be associated with an increased risk for the development of POPF.

Methods

A retrospective single-institution review was performed on all patients with PNET who underwent either pancreatic resection or enucleation from March 1998 to April 2010. One hundred twenty-two patients with PNET underwent 122 surgical procedures at the National Institutes of Health Clinical Center, Bethesda, MD. This study was approved by the Office of Human Subject Research at the National Institutes of Health. All participants provided informed written consent.

Variables evaluated for their association with development of POPF included age, gender, preoperative serum albumin level, body mass index (BMI) classification (kg/m^2) (normal ≤24.9, overweight 25–29.9, obese ≥30.0), if the tumor was functional or non-functional, and if the lesion was sporadic or, in the setting of an inherited genetic disease, known to be associated with increased risk of PNET. The PNET in patients with symptoms and biochemical evidence of hormone excess preoperatively were classified with standard techniques and diagnosed as functional tumors [15, 16, 23–29]. As much as 50–60 % of PNET are functionally active and secrete hormones in excess, including insulin, gastrin, somatostatin, vasoactive intestinal peptide (VIP), and, more rarely, adrenocorticotropic hormone (ACTH), and luteinizing hormone (LH) [15]. If there were no clinical symptoms of hormonal excess, and if plasma hormone levels were normal, the PNET was classified as non-functional. Patients with inherited genetic diseases, such as MEN-1 and VHL, were diagnosed based on clinical presentation, family history, and/or genetic testing [30]. All patients with MEN-1 were genetically tested for a mutation in the *MEN1* gene unless the patient was known to belong to a kindred with prior testing and had at least two clinical manifestations. Patients with VHL were tested for a mutation in the *VHL* gene.

All operative reports were reviewed in order to precisely determine the type of procedure performed and location of the lesions. An intraoperative ultrasound of the pancreas was routinely performed to assess the distance to the main pancreatic duct and evaluate the parenchyma for any additional lesions. All patients had a closed suction intra-operative drain placed at the pancreatic anastomosis, resection margin, or enucleation bed. Pathology reports were likewise reviewed to determine histology and confirm the size and number of lesions resected or enucleated.

The postoperative course for all patients was reviewed in order to determine the rate and appropriate classification of POPF. All patients' drain amylase levels were measured postoperatively. The ISGPF definition of drain amylase >3 times the normal serum amylase value on or after postoperative day 3 was used to determine POPF [3]. From strict ISGPF criteria, POPF were categorized as follows: grade A, an asymptomatic fistula with no interventions required, only elevated amylase from the drain fluid; grade B, a symptomatic fistula requiring a postoperative drain for >21 days, nonoperative intervention such as total parenteral nutrition (TPN), octreotide, percutaneous drain, or readmission within 30 days of hospitalization; and grade C, a severe fistula requiring surgical and nonoperative intervention, including reoperation, intensive care unit (ICU) care >48 h, or death within 30 days of operation. Our patients did not routinely receive perioperative octreotide as prophylaxis for the prevention of POPF.

Patient progress notes, discharge summaries, and clinic notes were used to determine the length of time the postoperative drain was in place and if any nonoperative interventions were required. Postoperative interventions evaluated included antibiotic use beyond the 24 h

perioperative period, presence of an infection confirmed with microbiology culture, blood product transfusion requirements, use of TPN or octreotide, imaging with computed tomography (CT), percutaneous drain placement, and any other postoperative complication.

Occasionally patients coming from outside the greater Washington DC area were discharged home with a surgical drain in place and returned to clinic between 3 and 6 weeks after surgery for their first postoperative check and possible surgical drain removal. Secondary to the time of their first postoperative clinic visit, some patients were placed in the grade B fistula category only because the surgical drain was kept in place for greater than 21 days. These patients did not meet any other criteria for a grade B POPF because they did not require nonoperative intervention, diet modification, readmission, or have prolonged hospital stays. These patients are similar to patients with asymptomatic grade A POPF. A recent study indicated that grade B and C POPF were clinically significant because they are associated with increased length of hospital stay and added cost [31]. In order to accurately report clinically significant POPF in our patient population, we divided the grade B patients into two cohorts for subgroup analysis: grade B1 patients were asymptomatic, did not require nonoperative interventions and only had a surgical drain in place >21-days because of travel constraints; grade B2 patients had symptomatic, clinically significant POPF, that required nonoperative interventions and had a surgical drain in place >21 days.

We analyzed the type of pancreatic procedure: enucleation or resection. Patients who underwent a pancreatectomy and enucleation in the same procedure were placed in the pancreatic resections group. An initial screening was performed in which Fisher's exact test was used to compare the frequencies of dichotomous clinical parameters according to each of the two classification groups, while the distribution of each of the continuous parameters was compared between the two groups of interest using an exact Wilcoxon rank sum test. Extent of surgery was compared between the two groups using a Cochran–Armitage test for trend. Any parameters found to have possible association with development of a fistula, as exhibited by having univariate p values <0.10 from the screening procedure, were further evaluated jointly in a multivariate logistic regression model when appropriate. All p values are two-tailed and univariate p values have not been formally adjusted for multiple comparisons. However, in view of the number of tests performed, only p values less than 0.01 should be interpreted as statistically significant. All data presented are median ± standard deviation except where otherwise specified.

Results

One hundred twenty-two patients had operations for PNET; 62 underwent pancreatic enucleation and 60 underwent pancreatic resection. The median age at the time of surgery was 42 years (range 11–78 years) with a slight female predominance 58.2 % (71/122). The patients had a median body mass index (BMI) of 28.7 kg/m^2 and a preoperative serum albumin level of 3.9 g/dL. Some 52.5 % (64/122) of the patients had an inherited genetic disease, and 63.1 % (77/122) had functional tumors (Table 1). There were 28 patients with MEN-1, 34 with VHL, one with neurofibromatosis (NF), and one with Birt–Hogg–Dubé syndrome. Our study had 53 insulinomas, 16 gastrinomas, one VIPoma, one somatostatinoma; one corticotropin releasing hormone (CRH) producing lesion, one adrenocorticotropic hormone (ACTH) producing lesion, one luteinizing hormone (LH) producing lesion, and one ectopic pheochromocytoma; one accessory spleen in a patient with a history of prior PNET; one pancreatic acinar carcinoma in a patient with VHL; and two microcystic adenomas in patients with VHL. There were 43 patients with nonfunctional PNET (Table 2).

The pancreatic enucleation and resection group were analyzed separately with the ISGPF criteria for POPF [3] (Table 3). The postsurgical outcomes data used to classify patients based on ISGPF criteria are shown in (Table 4). The 30 day mortality was less than 1 % (1/122 patients), and 6.6 % (8/122 patients) required a reoperation.

The 62 patients underwent pancreatic enucleation of 83 lesions. During a single procedure, 51 patients had one enucleation, 3 patients had two enucleations, 7 patients had three enucleations, and 1 patient had more than five lesions enucleated. Nine patients underwent a laparoscopic procedure and 53 patients underwent a laparotomy. The largest lesion was enucleated from the head of the pancreas in 42 patients and from the body or tail of the pancreas in 20 other patients (Table 5). The median size of the largest lesion enucleated was 1.8 ± 0.74 cm.

Sixty patients underwent a pancreatic resection for their PNET. Thirteen patients underwent a laparoscopic procedure and 47 underwent a laparotomy. These patients received a variety of pancreatic resections, including 39 distal pancreatectomy, 15 pancreaticoduodenectomy, 3 subtotal pancreatectomy, 1 total pancreatectomy, 2 pancreaticoduodenectomy and distal pancreatectomy. Of these 60 patients, 2 patients had simultaneous pancreaticoduodenectomy and distal pancreatectomy and 10 had a combined pancreatectomy and enucleation (Table 6). The median size of the largest lesion resected was 3.2 ± 2.5 cm.

In the enucleation group, the POPF were graded as follows: 25.8 % (16/62) grade A, 14.5 % (9/62) grade B1, 22.6 % (14/62) grade B2, and 4.8 % (3/62) grade C. Grade B and C POPF was found in 26 of 62 patients. Clinically significant POPF occurred in 14 patients with grade B2 and 3 patients with grade C, for a total rate of 27.4 % (17/62) (Table 7). A univariate analysis was done evaluating age, gender, albumin, BMI, type of procedure, number of lesions, size of largest lesion, location of lesion, histology, functionality of PNET, and inherited genetic diseases. Non-insulinoma tumors ($p = 0.02$) and inherited genetic diseases ($p = 0.02$) were associated with a higher POPF rate (Table 8). Based on the $p < 0.10$ threshold for evaluating parameters in a multivariate logistic model, histology, number of lesions, and inherited genetic disease type were considered as variables to be potentially evaluated relative to their association with development of a fistula. With a backward selection algorithm, it was determined that only inherited genetic diseases would be associated with fistula. This model was able to correctly classify 17/20 (85 %) patients without a fistula but only 20/42 with a fistula (48 %). Most patients (38/40) with insulinoma were sporadic, whereas almost all patients (21/22) with non-insulinoma tumors had an inherited disease and had a 1.5 times higher rate of POPF.

For the pancreatic resection group, the POPF were graded: 18.3 % (11/60) grade A, 18.3 % (11/60) grade B1, 16.7 % (10/60) grade B2, and 3.3 % (2/60) grade C. Grade B and C POPF was found in 23 of 60 patients. Clinically significant POPF occurred in 10 patients with grade B2 and 2 patients with gade C, for a total rate of 20 % (12/60 patients) (Table 7). A univariate analysis was conducted evaluating age, gender, albumin, BMI, transfusion, type of procedure, number of lesions, size of largest lesion, histology, functionality of PNET, and inherited genetic diseases. A BMI >25 ($p < 0.01$), MEN-1 ($p < 0.01$), and combined pancreatic resections and enucleation or simultaneous pancreaticoduodenectomy and distal pancreatectomy ($p = 0.02$) were associated with a higher POPF rate (Table 8). Those with a fistula also tended to have greater maximal lesion size (mean ± SEM = 3.75 ± 0.53 vs. 2.40 ± 0.20; $p = 0.067$), as well as larger actual BMI (31.79 ± 1.38 vs. 26.44 ± 1.01; $p = 0.011$). Using the $p = 0.10$ threshold from the screening procedure to determine which parameters to include in a multivariate logistic regression model, BMI, MEN-1 or not, VHL or not, extent of surgery (combined pancreatic resections and enucleation or simultaneous pancreaticoduodenectomy and distal pancreatectomy), and maximum lesion size were all

considered for inclusion in such a model. Based on a backward selection algorithm, a model with actual maximal lesion size and whether BMI was normal or not could be used to predict who would or would not have a fistula in the resection group.

Specifically, the model resulted in the following classification rule:

$$\text{Classify to fistula if} -3.1075\,(\text{if BMI is normal;0 if not}) + 0.4877 \times \text{max .lesion size} \geq 1.0.$$
$$\text{Classify to no fistula if} -3.1075\,(\text{if BMI is normal;0 if not}) + 0.4877 \times \text{max .lesion size} < 1.0.$$

Applying these rules to the data from which they were derived results in the following classification: 16/22 (68 %) without a fistula would be correctly identified, whereas 20/32 (63 %) with a fistula would be correctly identified. Further analysis of each surgical subgroup (enucleation and resection) was performed to identify if any surgical, clinical, or pathologic factors were predictive of severity of POPF. Risk factors were associated with the development of POPF but did not correlate with severity (grade A, B, or C) of fistula that developed. If patients who underwent combined procedures are excluded from the pancreatic resection group, there is still no difference in POPF between the groups. The POPF rate is 23 of 48 in the resection group and 26 of 62 in the enucleation group (p = 0.57).

Our clinically significant POPF rate for all procedures performed on PNET was 23.7 % (29/122). In the 122 patients, we identified 24 (16.4 %) grade B2 fistulas (14 enucleations and 10 resections) and 5 (4.1 %) grade C fistulas (3 enucleations and 2 resections). Patients who underwent pancreatic enucleation had a clinically significant POPF rate of 27.4 % (17/62), and those who underwent pancreatic resection had a POPF rate of 20 % (12/60). The difference in POPF was not significant (p = 0.4). Patient characteristics were analyzed separately by type of operation (resection vs. enucleation) (Table 8).

Discussion

Surgery is the only potentially curative option for PNET. Pancreatic fistula remains the most significant cause of postoperative morbidity and occasionally mortality in these patients who undergo pancreatic surgery. It is critical to elucidate risk factors that can predispose to severe fistula formation in this relatively rare inhomogeneous group. Our clinically significant POPF rate for all procedures performed on PNET was 23.7 % (29/122) with no difference between pancreatic resection and enucleation.

Because of our institutions' referral bias, we treat a large number of patients with MEN-1 and VHL. Our study showed a higher rate of POPF in patients with MEN-1 in the pancreatic resection group and VHL and MEN-1 patients in the pancreatic enucleation group. MEN-1 is an autosomal dominant syndrome associated with mutations in the *MEN1* gene, a tumor suppressor. Patients develop multiple neuroendocrine tumors within the pancreas, pituitary, and parathyroid glands and present with multiple PNET [23]. Von Hippel–Lindau disease is an autosomal dominant syndrome associated with mutations in the *VHL* tumor suppressor gene, which predisposes patients to neoplasms in a variety of organs, including the kidney (renal cell carcinoma), the adrenal gland (pheochromocytoma), the central nervous system (hemangioblastomas), the eye (retinal angioma), the inner ear (endolymphatic sac neoplasm), the epididymis (epididymal cystadenoma), and the pancreas (cystic lesions, cystic or serous cystadenomas, and PNET) [19]. Patients with MEN-1 and VHL have an increased risk for the development of PNET [19–21, 32]. Secondary to their increased risk of PNET, these patients undergo routine pancreatic computed tomography screening at our institution under an established clinical protocol. Patients with VHL and MEN-1 not only

can have multiple PNET, but VHL patients frequently have multiple cystic lesions in their pancreas [18–21, 33]. Their abnormal pancreatic parenchyma secondary to their underlying genetic defects and may contribute to a higher rate of POPF [18–21, 33].

In the pancreatic enucleation group, patients with non-insulinoma tumors had a higher POPF rate. However, 21 of 22 patients with non-insulinoma tumors had an inherited disease (VHL or MEN-1). It is difficult to ascertain if the non-insulinoma tumors, underlying genetic disease, or both account in part for the higher POPF rate, since 21 of 22 patients had both non-insulinoma tumors and an inherited genetic disease. Eleven patients underwent enucleation of more than one lesion during a single procedure. Enucleation of more than one lesion during a single procedure had a trend toward increased POPF rate but was not a factor found to be significant ($p = 0.09$). Most of these patients (9/11) had an inherited genetic disease, and that may be a contributing factor to the slightly higher POPF rate.

Patients in the pancreatic resection group with a BMI >25 and with larger lesions had an increased risk for the development of POPF. Body mass index >25 has been documented in the literature, for adenocarcinoma, as a risk factor for POPF [34]. However, BMI was not associated with POPF in the enucleation group.

A recent report [10] suggests that PNET are a risk factor for developing POPF when compared to procedures for pancreatic adenocarcinoma or chronic pancreatitis. These investigators found an increased risk for POPF with enucleation compared to resection. A previous study evaluated enucleation versus resection in small—less than 3 cm—peripancreatic or PNET and found a higher POPF rate in the enucleation group but no difference in the rate of severe POPF (grade B and C) between groups [12]. This is consistent with our data that show a clinically significant POPF (grade B2 and C) for enucleation of 27.4 % compared to 20 % in the resection group ($p = 0.4$), which is not statistically different.

Given the overall POPF rate in patients with PNET, it appears prudent that all patients have drains placed at the time of surgery. Our results are unlikely to change our practice of leaving a drain in every patient at the time of surgery. The data regarding octreotide as prophylaxis are conflicting; however, in patients with increased risk such as inherited genetic diseases such as MEN or VHL, BMI >25, non-insulinoma histology or combined pancreatic resection and enucleation, octreotide may be considered [35].

Data were collected on the surgical technique used to transect the pancreatic parenchyma in both the enucleation group and the resection group. There was a wide variety of techniques used, including electrocautery, harmonic scalpel, several different stapling devices, blunt dissection, and a combination of two or more. Various techniques were also used to close the pancreatic remnant in the distal pancreatectomies. Because of the retrospective nature of our study and varying surgical details, it is impossible to know what role these various techniques may have played in the POPF rate.

Other surgical techniques to reduce POPF have been described in the literature, such as the use of a Roux-en-Y limb to the enucleation bed or to the pancreatic margin in distal pancreatectomies [36]. Our institution has not employed these techniques, but they are worth considering in an attempt to decrease the POPF rate in both the resection and enucleation groups in patients with increased risk of POPF formation.

The overall POPF rate is relatively high in our patient population, all of whom underwent a pancreaticoduodenectomy, compared to the literature [8–12]. In our patients who underwent pancreaticoduodenectomy, 50 % (7/14) developed POPF, but 21.4 % (3/14) developed clinically significant POPF. The high overall POPF rate is likely due to the soft pancreatic

gland and non-dilated pancreatic duct in our patients. These characteristic have been shown to increase POPF after pancreaticoduodenectomy in patients with pancreatic adenocarcinoma [37–39].

Additionally, exact surgical technique used in the pancreaticojejunostomy anastomosis (duct to mucous vs. invagination technique) varied among surgeons and is a factor that could not be analyzed or factored into any risk model secondary to the small number of pancreaticoduodenectomies performed in our series [37, 40]. Regardless, the rate of clinically significant POPF in this series is similar to published literature for adenocarcinoma [8–12]. Pancreatic invagination technique for the pancreaticojejunostomy anastomosis could be considered in high-risk patients in the future.

Conclusions

The goal of the present study was to evaluate the clinically significant postoperative pancreatic fistula rates in patients with PNET following pancreatic enucleation and resection. Using the ISGPF criteria as a guide, we found the clinically significant rate of POPF for PNET of 23.7 %. There was no difference in clinically significant POPF rate between enucleation (27.4 % [17/62]) and resection (20 % [12/60]) ($p = 0.4$).

Patients with inherited diseases had a higher rate of POPF in both the enucleation and resection groups. Patients with inherited diseases may have a higher POPF rate because of their underlying abnormal pancreatic parenchyma. Patients with VHL frequently have multiple cystic lesions in their pancreas, and those with MEN-1 usually have multiple microscopic PNET [18–21, 33].

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Table 1

Demographics and clinical characteristics of study cohort

Variable	Enucleation (*n* = 62)	Resection (*n* = 60)	Total (*n* = 122)
Age, years, median ± (SD)	41.8 ± (16.3)	42.5 ± (13.1)	42.4 ± (14.8)
Gender			
Male	23 (37.1 %)	28 (46.7 %)	51 (41.8 %)
Female	39 (62.9 %)	32 (53.3 %)	71 (58.2 %)
BMI, kg/m^2, median (±SD)	27.6 ± (7.0)	29.0 ± (7.3)	28.7 ± (7.1)
Normal ≤24.9	16 (25.8 %)	18 (30 %)	34 (27.9 %)
Overweight 25.0–29.9	20 (32.2 %)	16 (26.7 %)	36 (29.5 %)
Obese ≥30.0	22 (35.4 %)	24 (40 %)	46 (37.7 %)
Sporadic	39 (62.9 %)	19 (31.7 %)	58 (47.5 %)
Inherited disease	23 (37.1 %)	41 (68.3 %)	64 (52.5 %)
MEN-1	9 (14.5 %)	19 (31.7 %)	28 (23 %)
VHL	14 (22.6 %)	20 (33.3 %)	34 (27.9 %)
Other	0 (0 %)	2 (3.3 %)	2 (1.6 %)
Non-functional	16 (25.8 %)	29 (48.3 %)	45 (36.9 %)
Functional	46 (74.2 %)	31 (51.7 %)	77 (63.1 %)
Preoperative serum albumin level, g/dL (SD)	3.9 ± (0.4)	4.0 ± (0.3)	3.9 ± (0.4)

BMI body mass index, *SD* standard deviation

Table 2

Types of pancreatic neuroendocrine tumors (PNET)

Histology	Enucleation (*n* = 62)	Resection (*n* = 60)	Total (*n* = 122)
Insulinoma	40 (64.5 %)	13 (21.7 %)	53 (43.4 %)
Gastrinoma	6 (9.7 %)	10 (16.7 %)	16 (13.1 %)
Somatostatinoma	0 (0 %)	1 (1.7 %)	1 (0.8 %)
VIPoma	0 (0 %)	1 (1.7 %)	1 (0.8 %)
Non-functional PNET	16 (25.8 %)	27 (45 %)	43 (35.2 %)
Other[a]	0 (0 %)	8 (13.3 %)	8 (6.6 %)

[a]Corticotropin releasing hormone (CRH) producing lesion, one ACTH producing tumor, one leuteinizing hormone producing tumor, one ectopic pheochromocytoma, one pancreatic acinar carcinoma, two microcystic adenomas, one accessory spleen in a patient with a history of prior PNET

Table 3

Pancreatic fistula grade criteria suggested by Study Group of Pancreatic Fistula (IGSPF)

Criteria	No. fistulas	Grade A	Grade B	Grade C
Drain amylase	<3 × Normal serum amylase	>3 × Normal serum amylase	>3 × Normal serum amylase	>3 × Normal serum amylase
Drain >21 days	No	No	Yes	Yes
Clinical condition	Well	Well	Well	Sick
US/CT (if obtained)	Negative	Negative	Negative/positive	Positive
Percutaneous drain	No	No	Yes/no	Yes/no
Nonoperative specific treatments	No	No	Yes/no	Yes
Signs of infection	No	No	Yes/no	Yes
Sepsis	No	No	No	Yes
Reoperation	No	No	Yes/no	Yes
Readmission	No	No	Yes/no	Yes
Death related to fistula	No	No	No	Yes

Table 4

Post surgical outcomes

Factors	Enucleation (*n* = 62)	Resection (*n* = 60)	Total (*n* = 122)
Readmission	12 (19.4 %)	9 (15 %)	21 (17.2 %)
Drain amylase[a]	6,717 (13–510,300)	1,389 (9–95,574)	2,776 (13–510,300)
No. of patients with drain amylase >3 × normal	40 (64.5 %)	35 (58.3 %)	74 (60.7 %)
Days for postoperative drain[a]	15.5 (3–200)	15 (3–84)	15 (3–200)
No. of patients with drain >21 days	24 (38.7 %)	21 (35 %)	44 (36.1 %)
ICU care >48 h	3 (4.8 %)	2 (3.3 %)	5 (4.1 %)
Postoperative CT scan			
None	22 (35.5 %)	29 (48.3 %)	51 (41.8 %)
Negative	23 (37.1 %)	18 (30 %)	43 (35.2 %)
Positive	17 (27.4 %)	13 (21.7 %)	30 (24.6 %)
Percutaneous drain	12 (19.4 %)	9 (15 %)	20 (16.4 %)
TPN	13 (21 %)	9 (15 %)	22 (18 %)
Octreotide	14 (22.6 %)	15 (25 %)	29 (23.8 %)
Transfusion	8 (12.9 %)	8 (13.3 %)	16 (13.1 %)
Antibiotics	28 (45.2 %)	23 (38.3 %)	51 (41.8 %)
Positive culture[b]	19 (30.6 %)	15 (25 %)	34 (27.9 %)
Sepsis	2 (3.2 %)	0 (0 %)	2 (1.6 %)
Reoperation	5[c] (8 %)	3 (5 %)	8 (6.6 %)
Death within 30 days	1 (1.6 %)	0 (0 %)	1 (0.8 %)

ICU intensive care unit; *CT* computed tomography; *TPN* total parental nutrition

[a] Median (range)

[b] Postive culture from blood, urine, wound, or drain

[c] One patient underwent reoperation for internal hernia; one patient underwent reoperation for removal of another lesion

Table 5

Pancreatic enucleation

Type of operation	Patients (*n* = 62)
Laparoscopic	9 (14.5 %)
Exploratory laparotomy	53 (85.5 %)
Number of lesions enucleated	
1	51 (82.3 %)
2	3 (4.8 %)
3	7 (11.3 %)
>3	1 (1.6 %)
Location of largest lesion	
Head	42 (67.7 %)
Body or tail	20 (32.3 %)

Table 6

Pancreatic resection

Type of operation	Patients (*n* = 60)
Laparoscopic	13 (21.7 %)
Exploratory laparotomy	47 (78.3 %)
Distal pancreatectomy	39 (65 %)
Pancreaticoduodenectomy	15 (25 %)
Subtotal pancreatectomy	3 (5 %)
Total pancreatectomy	1 (1.7 %)
Pancreaticoduodenectomy and distal pancreatectomy	2 (3.3 %)
Any pancreatectomy with enucleation	10 (16.7 %)

Table 7

Pancreatic fistula rates

Fistula grade	Enucleation (n = 62)	Resection (n = 60)	All (n = 122)	p Value
No fistula	20 (32.3 %)	26 (43.3 %)	46 (37.7 %)	
Grade A	16 (25.8 %)	11 (18.3 %)	27 (22.1 %)	
Grade B	23 (37.1 %)	21 (35 %)	44 (36.1 %)	
B1	9 (14.5 %)	11 (18.3 %)	20 (16.4 %)	
B2	14 (22.6 %)	10 (16.7 %)	24 (19.7 %)	
Grade C	3 (4.8 %)	2 (3.3 %)	5 (4.1 %)	
Clinically significant fistula				
Grade B2	14 (22.6 %)	10 (16.7 %)	24 (19.7 %)	
Grade C	3 (4.8 %)	2 (3.3 %)	5 (4.1 %)	
All	17 (27.4 %)	12 (20 %)	29 (23.8 %)	0.4

Table 8

Univariate analysis of factors associated with postoperative pancreatic fistula (POPF)

Pancreatic enucleation				**Pancreatic resection**			
Variable	**No fistula**	**Grade A, B, C**	***p* Value**	**Variable**	**No fistula**	**Grade A, B, C**	***p* Value**
Gender			0.26	Gender			0.44
Male	5	18		Male	10	17	
Female	15	24		Female	16	17	
BMI			0.22	BMI			0.004
≤24	7	9		≤24	12	28	
>25	11	31		>25	13	5	
Obese			1.00	Obese			0.28
≤29	11	25		≤29	17	17	
>30	7	15		>30	8	16	
Inherited disease			0.023	Inherited disease			0.78
No	17	22		No	9	10	
Yes	3	20		Yes	17	24	
MEN-1			0.048	MEN-1			0.0047
No	20	33		No	23	18	
Yes	0	9		Yes	3	16	
VHL			0.52	VHL			0.098
No	17	31		No	14	26	
Yes	3	11		Yes	12	8	
Functional			0.35	Functional			0.20
No	3	12		No	15	13	
Yes	17	30		Yes	11	20	
No. of lesions			0.09	No. of lesions			0.52
1	19	32		1	17	28	
2+	1	10		2+	6	6	
Transfusion			1.00	Transfusion			0.45
No	18	36		No	23	28	
Yes	2	6		Yes	2	6	
Size			1.00	Size			0.73

Pancreatic enucleation				Pancreatic resection			
Variable	**No fistula**	**Grade A, B, C**	***p* Value**	**Variable**	**No fistula**	**Grade A, B, C**	***p* Value**
≤1.5 cm	5	12		≤1.5 cm	3	6	
>1.5 cm	15	30		>1.5 cm	19	27	
Albumin			0.24	Albumin			0.17
≤3.6 g/dl	8	12		≤3.6 g/dl	2	8	
>3.7 g/dl	10	31		>3.7 g/dl	22	26	
Surgery			0.45	Surgery			0.021
Laparoscopic	4	5		Distal pancreatectomy	18	16	
Laparotomy	16	37		Whipple	7	7	
Histology			0.025	Combined[a]	1	11	
Insulinoma	17	23					
Other	3	19					
Location			1.00				
Head	14	28					
Non-head	6	14					

BMI body mass index, *MEN-1* multiple endocrine neoplasia type 1, *VHL* von Hippel–Lindau disease

[a]Combined pancreatectomy and enucleation or combined pancreaticoduodenectomy and distal pancreatectomy