ORIGINAL ARTICLE

Pancreatic fistulae after pancreatic resections for neuroendocrine tumours compared with resections for other lesions

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Abstract

Background: Resection for pancreatic neuroendocrine tumours (PNET) is suggested to be associated with an increased risk of a post-operative pancreatic fistula (POPF). The aim of this study was to describe morbidity after resections for PNET, focusing on POPF. Outcomes were compared with resections for other lesions.

Methods: Patients undergoing an elective pancreatic resection during a 12-year period were retrospectively analysed. Morbidity was defined according to the International Study Group of Pancreatic Surgery (ISGPS) definitions.

Results: Eighty-eight out of 832 patients (10.6%) underwent a resection for PNET. Atypical pancreatic resections (enucleation and central pancreatectomy) and distal pancreatectomies were more frequently performed for PNET. The POPF rate was 22.7% in patients operated for PNET compared with 17.2% in other patients ($P = 0.200$). In univariate analysis, body mass index (BMI), pancreatic duct diameter, somatostatin analogue administration, type of resection and type of pathology were associated with a POPF. In multivariate analysis, BMI, a pancreatic duct diameter <3 mm and central pancreatectomy remained independent risk factors [odds ratio (OR) 1.93, 95% confidence interval (CI) 1.22–3.07 and OR 3.04, 95% CI 1.05–8.82, respectively].

Conclusions: High rates of POPF were found in patients operated for PNET. However, this was mainly owing to the fact that atypical resections, known to be associated with a higher fistula rate, were performed more frequently in these patients.

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Introduction

Pancreatic neuroendocrine tumours (PNET) are malignancies of the pancreas with a reported incidence of <1 per 100 000 persons per year.[1] Although PNET only comprise approximately 3% of all pancreatic neoplasms, autopsy studies have indicated that PNET are much more common; incidence rates up to 10% in patients undergoing extensive pathological post-mortem examination are described.[2,3] Furthermore, the incidence is increasing, partly explained by growing numbers of incidentally detected PNET owing to the more frequent use of imaging.[1,4–6]

PNET can be divided into functional and non-functional tumours (NF-PNET). Functional PNET secrete hormones, such as insulin, gastrin and glucagon, all causing a specific hormonal syndrome. Non-functional tumours, estimated to make up 90% of all PNET, are not associated with a specific hormonal syndrome either because no peptide is secreted or the secreted substance does not cause any symptoms.[1]

In contrast to pancreatic adenocarcinoma, most PNET have an indolent tumour biology. Nevertheless, surgery is the treatment of choice for resectable disease and selected cases with resectable metastases.[7–11] However, controversy remains regarding several surgical aspects of PNET, such as the role of atypical resections

(enucleations and central pancreatectomies), resection of the PNET primary in case of metastases and the surgical management of possibly benign, small (<2 cm) NF-PNET.[11–16]

An important determinant in the surgical approach of patients with PNET is post-operative morbidity. Although mortality after a pancreatic resection has decreased below 5% in high-volume centres, morbidity remains high (40–70%).[17,18] A post-operative pancreatic fistula (POPF) is one of the most frequent, potentially life-threatening complications and can originate from the pancreatic remnant after a distal pancreatectomy (DP) or enucleation, as well as from an anastomosis such as the pancreaticojejunostomy or pancreatico-gastrostomy.[19] Several histomorphological features of the pancreas have been associated with POPF. Soft consistency of the pancreatic parenchyma is regarded as a risk factor for fistula development, as well as small pancreatic duct size and fatty pancreas.[20–24] Underlying pathology is also correlated with the incidence of POPF as adenocarcinoma and chronic pancreatitis are typically associated with firm, fibrotic and thereby easily sutured glands, whereas other peri-ampullary cancers and benign processes are associated with a soft gland.[20,21] PNET rarely cause duct dilatation and fibrosis, and could therefore be associated with increased rates of POPF.[8,20,21,25]

In this study, we describe a cohort of patients undergoing a resection for PNET at a referral centre for pancreatic lesions. Post-operative morbidity is compared between patients operated for PNET and patients undergoing a pancreatic resection for other diseases, with special interest in the incidence of a pancreatic fistula.

Patients and methods

A consecutive series of patients undergoing an elective pancreatic resection during a 12-year period at a tertiary referral centre was analysed. Local pancreatic head resections combined with a pancreaticojejunostomy for chronic pancreatitis and total pancreatectomies were excluded. Furthermore, pancreatic tail resections, as part of extended oncological multivisceral resections (e.g. for stomach or colonic cancer), as well as pancreatic resections for abdominal trauma were also excluded.

Data concerning patients treated with a pancreatoduodenectomy (PD) were gathered from a prospectively registered database. Patients undergoing other types of pancreatic resection were identified using electronic administrative databases and data were retrospectively collected. The clinical records of all patients were analysed with regard to fulfilling the criteria of this study. Clinicopathological data, demographics and post-operative outcomes were assessed. Main pancreatic duct diameter and size of neuroendocrine tumours were based upon measurements on pre-operative computed tomography. In case of multiple neuroendocrine lesions, the size of the largest lesion was noted.

Because the present study involved a retrospective analysis of anonymized data, the Dutch Ethical Review Board regulations do not require informed consent.

Surgical procedures

The standard surgical procedure for suspected malignancy (including grade 3 neuroendocrine neoplasms) of the pancreatic head was a pylorus-preserving PD with removal of the lymph nodes on the right side of the portal vein, as described earlier.[26,27] In case of tumour ingrowth in the pylorus or duodenum, a classic Whipple's resection was performed. Reconstruction was performed by end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy and a duodeno – or gastrojejunostomy on the same jejunal limb, without Roux-en-Y reconstruction. Lesions of the pancreas body and/or tail were treated with a DP with or without spleen preservation. The decision to include a splenectomy was made intra-operatively, taking into account the patient's underlying disease as well as the curative intention. The pancreatic remnant was closed either by stapler or hand-sewn, depending on the patients participation in a trial, or the surgeons preference.[28] A central pancreatectomy (CP), also known as a middle or median pancreatectomy, was performed only for small benign or low-grade malignant neoplasms and metastases from extrapancreatic malignancies (renal cell carcinoma), located in the pancreatic body. The transected pancreatic head was stapled or sutured and an end-to-side Roux-en-Y pancreaticojejunostomy was anastomosed to the pancreatic tail. Enucleation was considered for superficial insulinomas, non-functioning tumours smaller than 2 cm and small cystic neoplasm, taking into account that the main pancreatic duct could safely be preserved. When in doubt, an intra-operative ultrasonography was performed. On occasion, an absorbable fibrin sealant patch was used if there was a high anticipated risk of a post-operative pancreatic fistula.

A prophylactic, intraperitoneal drain was placed routinely after all pancreatic resections (except after enucleations) and was generally removed after 4–5 days, earlier if output had ceased and the condition of the patient justified its removal. Somatostatin analogues (100 μg subcutaneously 3 times/day) or long-acting somatostatin analogues (120 mg intragluteal 1/28 days) were administered prophylactically to patients at risk of developing a pancreatic fistula (non-dilated pancreatic duct and/or soft pancreatic tissue), and as short-time treatment for an established POPF.

Underlying disease

The diagnosis of the underlying disease was based upon histopathology reports. Neuroendocrine tumours were considered non-functional if no clinical symptoms of hormonal excess were present. Insulinomas were biochemically diagnosed using a 72-h supervised fasting test. The diagnosis of gastrinoma was established by measuring elevated fasting gastrin levels. VIPoma was confirmed by raised serum vasoactive intestinal peptide levels. Patients were considered as having carcinoid syndrome if tumour symptoms were accompanied with evidence of serotonin, tachykinin or prostaglandin secretion.

Outcome measures

Primary evaluated outcome was morbidity after surgery. A POPF, delayed gastric emptying (DGE) and a post-operative haemorrhage (PPH) were defined according to the International Study Group of Pancreatic Surgery (ISGPS) definitions.[29–31] For these specific complications, grades B and C were considered clinically relevant. An abdominal abscess was defined as a fluid collection with positive bacterial culture. Other peri-operative outcome parameters were: the need for reoperation, duration of hospital stay, readmission within 30 days and peri-operative mortality defined as death in hospital.

Statistical analysis

For all statistical analyses PASW Statistics 18.0.2 was used (SPSS Inc, Chicago, IL, USA).

Results are presented as mean ± SD or median with interquartile range (IQR) depending on the distribution of the data. Comparison between patients with PNET and patienta with other indications for a pancreatic resection was performed using the χ^2 test or Fisher's exact test for categorical data, and the independent t-test or the Mann–Whitney U-test for continuous data, depending on the distribution. Univariate logistic regression analysis was performed to identify risk factors for the development of a pancreatic fistula. Factors with a P-value of ≤0.20 and factors with clinical plausibility for impacting outcome were considered for inclusion in multivariate regression analysis. In order to include all patients in the multivariate analysis, missing values of body mass index (BMI) and pancreatic duct size were imputed using multiple imputation with a creation of five datasets. Multivariate logistic regression analysis was done in the five imputed datasets and the outcomes were pooled. Results are shown as odds ratio's (OR) and 95% confidence intervals (CI). In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

During the study period, 832 consecutive patients underwent an elective pancreatic resection and fulfilled the inclusion criteria. Of these, 88 patients (10.6%) underwent a surgical resection for PNET. The remaining 744 patients underwent an elective pancreatic resection for other diseases (Table 1).

Of the 88 patients undergoing a resection for PNET, 64 patients had a PNET defined as non-functional (72.7% of PNET). Twenty-four patients had functioning neuroendocrine tumours (27.3%):

Table 1 Patient and operative characteristics of 88 patients with PNET and 744 patients with other diseases undergoing a pancreatic resection

	PNET (n = 88)	Other (n = 744)	Total (n = 832)	P-value
Age – Mean (SD)	55 (13.8)	62 (12.4)	61 (12.7)	*0.001*
Male gender – No (%)	39 (44.3)	410 (55.1)	449 (54.0)	0.055
ASA classification – No (%)				
I	20 (22.7)	152 (20.4)	172 (20.7)	0.960
II	59 (67.0)	466 (62.6)	525 (63.1)	0.211
III/IV	9 (10.2)	126 (16.9)	135 (16.2)	0.088
Body Mass Index (kg/m^2) – Mean (SD)	25.8 (4.4)[a]	24.6 (4.1)[a]	24.8 (4.1)	*0.047*
Comorbidity – No (%)				
Cardiac	11 (12.5)	152 (20.4)	163 (19.6)	0.142
Diabetes mellitus	11 (12.5)	132 (17.7)	143 (17.2)	0.094
Hypertension	19 (21.6)	192 (25.8)	211 (25.4)	0.273
Pulmonary	4 (4.5)	73 (9.8)	77 (9.3)	0.082
Pancreatic duct diameter < 3 mm – No (%)	68 (77.3)	334 (47.7)[b]	402 (48.3)	*<0.001*
Somatostatin analogue administration – No (%)	51 (58.0)	369 (49.6)	420 (50.5)	0.138
Surgical procedure – No (%)				
Central pancreatectomy	9 (10.2)	11 (1.5)	20 (2.4)	*<0.001*
Distal pancreatectomy	26 (29.5)	113 (15.2)	139 (16.7)	*<0.001*
Spleen preserving (% of DP)	15 (57.7)	45 (39.8)	60 (43.2)	0.097
Enucleation	24 (27.3)	4 (0.5)	28 (3.4)	*<0.001*
Pancreatoduodenectomy	29 (33.0)	616 (82.8)	645 (77.5)	*<0.001*
Pylorus-preserving (% of PD)	24 (82.8)	546 (88.6)	570 (88.4)	0.335

P-values highlighted in bold and italicized are considered to indicate statistical significance.
[a]For 64 (72.7%) and 496 patients (66.7%) data for calculation of BMI were available.
[b]For 269 patients (80.5%) data on pancreatic duct size were available.
PNET, pancreatic neuroendocrine tumour; SD, standard deviation; ASA, American Society of Anesthesiologists; PD, pancreatoduodenectomy; DP, distal pancreatectomy.

insulinomas (18/88; 20.5%), gastrinomas (3/88; 3.4%), carcinoids (2/88; 2.3%) and VIPoma (1/88; 1.1%). Of the PNET, 52/88 (59.1%) were classified as grade 1, 25/88 (28.4) as grade 2 and 5/88 tumours (5.7%) were classified grade 3.[26] The remaining six tumours (6.8%) could not be classified. The median PNET size was 21 mm (range 7–150).

Seven hundred forty-four patients (89.4%) underwent a pancreatic resection for other diseases. Two hundred forty-four patients (29.3%) had pancreatic adenocarcinoma as the underlying disease and eighty-six patients (10.3%) had chronic pancreatitis. One hundred and forty-one patients (17.3%) had miscellaneous pancreatic diseases: serous and mucinous cystadenomas (35 and 22), intraductal papillary mucinous neoplasms (48), metastases from extrapancreatic malignancies (15), solid pseudopapillary neoplasms (6) and other pancreatic indications (15). The remaining 273 (32.8%) patients were operated for non-pancreatic diseases: 135 (16.2%) ampullary carcinoma, 93 (11.2%) distal cholangiocarcinoma and 45 (5.4%) miscellaneous non-pancreatic indications.

Patients undergoing a resection of PNET were significantly younger and had a higher BMI compared with the other patients. Furthermore, a small pancreatic duct size (<3 mm) was more frequently found in patients with PNET.

Surgical procedures

Surgical procedures performed were 645 pancreatoduodenectomies (77.5%), 139 distal pancreatectomies (16.7%), 20 central pancreatectomies (2.4%) and 28 enucleations (3.4%). Regarding distal pancreatectomies, the pancreas was transected using a stapling device in 66 patients (47.5%), whereas the pancreatic remnant was hand-sewn in 61 patients (43.9%). Five patients (3.6%), all with chronic pancreatitis, had a pancreaticojejunostomy anastomosed to the pancreatic head. In 7 patients (5.0%), the technique of closure of the pancreatic remnant was unknown. After a central pancreatectomy, the head was closed using staples in 15 patients (75.0%) and hand-sewn in five (25.0%), the pancreatic tail was reconstructed with a pancreaticojejunostomy in all patients. Three distal pancreatectomies were performed laparoscopically (2.2%). In seven patients (4 distal pancreatectomies and 3 enucleations), an absorbable fibrin sealant patch was applied after a pancreatic resection.

Enucleations, central pancreatectomies and distal pancreatectomies were more often performed for neuroendocrine tumours, whereas a pancreatoduodenectomy was less frequently performed.

Post-operative outcome

The overall morbidity and mortality rate was 54.6% and 2.2%, respectively (Table 2). Surgery-related complications occurred in 391 patients (47.0%). The median length of hospital stay was 11 days. A clinically relevant POPF was the most frequent surgical complication after a resection for PNET (22.7%). In the group undergoing a pancreatic resection for other indications, and the

Table 2 Post-operative complications and other outcomes in patients undergoing a pancreatic resection for PNET ($n = 88$) and other diseases ($n = 744$)

	PNET ($n = 88$)	Other ($n = 744$)	Total ($n = 832$)	*P*-value
Any complication – No (%)	41 (46.6)	413 (55.5)	454 (54.6)	0.112
Surgical complications – No (%)	38 (43.2)	353 (47.4)	391 (47.0)	0.448
Pancreatic fistula grade B/C[a]	20 (22.7)	128 (17.2)	148 (17.8)	0.200
Delayed gastric emptying grade B/C[a]	11 (12.5)	209 (28.1)	220 (26.4)	*0.002*
Post-pancreatectomy haemorrhage grade B/C [a]	6 (6.8)	37 (5.0)	24 (4.3)	0.460
Wound infection	3 (3.4)	74 (9.9)	77 (9.3)	0.050
Other	10 (11.4)	72 (9.7)	82 (9.9)	0.616
Non-surgical complications – No (%)	12 (13.6)	172 (23.1)	184 (22.1)	*0.043*
Cardiac	3 (3.4)	46 (6.2)	49 (5.9)	0.469
Pneumonia	2 (2.3)	39 (5.2)	41 (4.9)	0.302
Other pulmonary	5 (5.7)	60 (8.1)	65 (7.8)	0.431
Urinary tract infection	4 (4.5)	55 (7.4)	59 (7.1)	0.507
Other	3 (3.4)	58 (7.8)	61 (7.3)	0.191
In-hospital mortality – No (%)	2 (2.3)	16 (2.2)	18 (2.2)	1.000
Reoperation – No (%)	6 (6.8)	59 (7.9)	65 (7.8)	0.713
Length of hospital stay in days – Median (IQR)	11 (10)	11 (9)	11 (9)	0.255
Hospital readmission within 30 days – No (%)	10 (11.4)	76 (10.2)	86 (10.3)	0.738

P-values highlighted in bold and italicized are considered to indicate statistical significance.
[a]According to the International Study Group of Pancreatic Surgery definition.
PNET, pancreatic neuroendocrine tumour; IQR, interquartile range; PJ, pancreaticojejunostomy.

overall group, clinically relevant DGE had the highest incidence (28.1% and 26.4%, respectively).

POPF

The overall clinically relevant pancreatic fistula rate was 17.8% and did not change significantly during the study period. The POPF rate subdivided according to type of underlying pathology and type of pancreatic resection is shown in Table 3, The highest rate of POPF was seen in patients operated for ampullary carcinoma (24.4%), whereas patients operated for pancreatic adenocarcinoma had the lowest fistula rate (9.0%). Of the 88 patients with a neuroendocrine tumour, 20 (22.7%) developed a grade B or C POPF. Regarding type of resection, enucleation and a central pancreatectomy were significantly associated with high rates of POPF (35.7% and 40.0%, respectively) compared with a pancreatoduodenectomy (17.7%) and distal pancreatectomy (11.5%) ($P \leq 0.001$).

In univariate analysis, BMI, pancreatic duct diameter, somatostatin analogue administration, type of resection and type of underlying pathology were associated with the risk of developing a pancreatic fistula (Table 4). In multivariate analysis, BMI, pancreatic duct diameter <3 mm and a central pancreatectomy remained independent risk factors for the development of a POPF (OR 1.93, 95% CI 1.22–3.07 and OR 3.04, 95% CI 1.05–8.82, respectively). PNET as underlying pathology was not associated with post-operative fistula development.

Table 3 Post-operative pancreatic fistula rate subdivided according to type of underlying pathology and type of pancreatic resection (n = 832)

	Pancreatic fistula (ISGPS grade B/C) – n (%)
Type of underlying pathology	
Ampullary carcinoma	33/135 (24.4)
Chronic pancreatitis	13/86 (15.1)
Distal cholangiocarcinoma	22/93 (23.7)
Miscellaneous non-pancreatic disease	13/45 (28.9)
Miscellaneous pancreatic disease	25/141 (17.7)
Pancreatic adenocarcinoma	22/244 (9.0)†
PNET	20/88 (22.7)
Type of resection	
Central pancreatectomy	8/20 (40.0)‡
Distal pancreatectomy	16/139 (11.5)
Enucleation	10/28 (35.7)‡
PD/PPPD	114/645 (17.7)
Total	148/832 (17.8)

†$P \leq 0.05$ versus all other pathologies except chronic pancreatitis.
‡$P \leq 0.05$ versus PD/PPPD and versus distal pancreatectomy.
PNET, pancreatic neuroendocrine tumour; PD, pancreatoduodenectomy; PPPD, pylorus-perserving pancreatoduodenectomy.

Subanalysis of patients undergoing a pancreatoduodenectomy

When only patients who underwent a pancreatoduodenectomy (n = 645) were analysed, BMI, pancreatic duct diameter and type of underlying pathology were associated with fistula development in univariate analysis. In multivariate analysis, only BMI and pancreatic duct diameter remained independently associated with a POPF (OR 1.11, 95% CI 1.04–1.18 and OR 2.09, 95% CI 1.28–3.41, respectively).

Discussion

In this study, a consecutive series of 88 patients with PNET undergoing a resection during a 12-year period at a tertiary referral centre was analysed. Mortality and morbidity was compared with 744 patients undergoing pancreatic resections for other indications during the same period. The overall morbidity and mortality was 54.6% and 2.2%, respectively. Patients operated for PNET did not show a significantly higher pancreatic fistula rate compared with patients operated for other diseases (22.7% versus 17.2%, $P = 0.200$). The type of underlying pathology was not in independent risk factor for fistula development, except for a lower fistula rate after a resection for pancreatic adenocarcinoma. A central pancreatectomy, known to be associated with fistula development and more frequently performed for neuroendocrine tumours, was independently associated with a POPF, along with a pancreatic duct diameter <3 mm and BMI.

The overall incidence of clinically relevant POPF (ISGPS grade B/C) was 17.8%. The highest incidence of fistula development was seen in patients operated for miscellaneous non-pancreatic diseases (13/45, 28.9%), followed by ampullary carcinoma (33/135, 24.4). The lowest fistula rate was seen in patients undergoing pancreatic resections for pancreatic adenocarcinoma (9.0%) and chronic pancreatitis (15.1%). This is in line with previous reports describing lower fistula rates after resections for pancreatic adenocarcinoma and chronic pancreatitis, in which the pancreatic parenchyma is fibrotic and firm, and the pancreatic duct is frequently dilated.[32] Pancreatic lesions that usually do not cause fibrotic reactions, such as PNET are generally not associated with pancreatic duct obstruction. High fistula rates after resections for PNET have been described accordingly.[25,33]

The type of pancreatic resection was strongly associated with post-operative fistula development. Patients undergoing a central pancreatectomy and enucleation had POPF rates of 40.0% and 35.7%, respectively. The high rate of pancreatic fistula after a central pancreatectomy, in which there are two transected pancreatic surfaces, has been widely acknowledged and many series report fistula rates greater than 30%.[34–37] High rates of pancreatic fistula after enucleation have also been reported.[38] However, in line with our data, enucleation is not always found to be an independent predictor of fistula formation.[33,39]

In our study, multivariate analysis identified BMI, a pancreatic duct diameter <3 mm and a central pancreatectomy as

Table 4 Univariate and multivariate logistic regression analysis of patient- and surgery-related risk factors for a post-operative pancreatic fistula (ISGPS grade B/C)

	Univariate	Multivariate		
	P-value	Odds ratio	95% CI interval	*P*-value
Age >59 years	0.889	–	–	–
Male gender	0.351	–	–	–
Body Mass Index (kg/m²)[a]	<0.001	1.12	1.06–1.19	<0.001
ASA classification	0.725	–	–	–
I	ref	–	–	–
II	0.760	–	–	–
III/IV	0.660	–	–	–
Comorbidity				
Cardiac	0.493	–	–	–
Diabetes mellitus	0.812	–	–	–
Hypertension	0.470	–	–	–
Pulmonary	0.303	–	–	–
Pancreatic duct diameter <3 mm[b]	<0.001	1.93	1.22–3.07	0.005
Somatostatin analogue administration	0.026	0.93	0.62–1.39	0.723
Type of resection	0.002	–	–	–
PD/PPPD	ref	ref	ref	ref
Central pancreatectomy	0.015	3.04	1.05–8.82	0.041
Distal pancreatectomy	0.079	0.64	0.32–1.26	0.197
Enucleation	0.020	2.21	0.77–6.29	0.140
Type of underlying pathology	0.001	–	–	–
PNET	ref	ref	ref	ref
Ampullary carcinoma	0.768	2.17	0.91–5.13	0.079
Chronic pancreatitis	0.203	1.41	0.55–3.63	0.474
Distal cholangiocarcinoma	0.882	1.67	0.68–4.07	0.261
Miscellaneous pancreatic disease	0.356	1.16	0.53–2.43	0.710
Miscellaneous non-pancreatic disease	0.437	2.24	0.81–6.18	0.119
Pancreatic adenocarcinoma	0.001	0.75	0.32–1.80	0.525

[a]For 560 patients (67.3%) data for calculation of BMI were available.
[b]For 767 patients (92.2%) data regarding pancreatic duct diameter were available.
ASA, American Society of Anesthesiologists; PD, pancreatoduodenectomy; PPPD, pylorus-perserving pancreatoduodenectomy; PNET, pancreatic neuroendocrine tumour.

independent risk factors for the development of clinically relevant POPF. The type of underlying disease was not independently associated with POPF; we could not identify a neuroendocrine tumour as an independent risk factor for fistula development, as described earlier.[25] The use of somatostatin analogues was not independently associated with POPF either. Although clear evidence is lacking, usage of somatostatin analogues in a risk-dependant manner might be beneficial.[40] The association of small pancreatic duct size and high BMI with POPF development is in line with previous reports.[32,41,42]

PNET are a diverse group of malignancies which compromise only a small portion of all pancreatic neoplasms. Presentation and prognosis differs considerably between types of PNET. However for all types of PNET resection provides the only chance of a cure

and is the treatment of choice. Controversy remains regarding several surgical aspects: for small (<2 cm) non-functional neuroendocrine tumours, a non-operative approach can be advocated and current guidelines recommend considering short- and long-term sequelae of pancreatic resections in choosing the appropriate treatment.[11] As improved imaging techniques contribute to growing incidence rates of small NF-PNET, this dilemma is of increasing relevance. Correct patient selection is paramount in order to optimize treatment results, especially because pancreatic resections are still associated with high post-operative morbidity. Another important aspect of pancreatic surgery is the possibility to perform parenchyma-preserving resections. These procedures can successfully lower the risk of developing pancreatic endocrine and exocrine insufficiency.[43–45]

An increased risk of developing a pancreatic fistula after parenchyma-preserving resections was shown, but these finding can merely aid the decision-making process in choosing the appropriate treatment.

This study has several limitations. Because of its retrospective design regarding patients undergoing atypical resections and the varying surgical details, we could not study the effect of various resection and closure techniques which have been described in an attempt to reduce the fistula rate. However, a large randomized trial comparing stapler versus hand-sewn closure did not find any effect and large comparative trials have yet to be published regarding other closure techniques.[28,46–49] Data regarding pancreatic hardness were also lacking. Although experts agree that a 'soft' pancreas is a risk factor for fistula formation, there is no clear definition. Palpatory assessment by experienced surgeons is suggested to correlate well with quantitative measurements of pancreatic hardness by durometre, although this has to be confirmed in large studies.[50] Furthermore, we did not assess long-term pancreatic insufficiency, nor have we investigated survival. In spite of these shortcomings, this study reports a large consecutive cohort of pancreatic resections for PNET and other lesions from a single institution, applying generally accepted ISGPS definitions of outcomes after pancreatic surgery.

In conclusion, this study describes a consecutive series of patients undergoing a resection for PNET at a single centre and compares outcomes with patients undergoing a resection for other diseases. Although a high pancreatic fistula rate was seen in patients operated for PNET, this was due to the fact that atypical resections such as central pancreatectomy and enucleation, which are known to be associated with fistula development, were performed more frequently in these patients. A neuroendocrine tumour as underlying pathology was not independently associated with fistula development.

Conflicts of interest
None declared.

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