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ORIGINAL ARTICLE

Indications for resection and perioperative outcomes of surgery for pancreatic neuroendocrine neoplasms in Germany: an analysis of the prospective DGAV StuDoQ|Pancreas registry

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Abstract

Purpose Pancreatic neuroendocrine neoplasms (pNENs) are rare, and their surgical management is complex. This study evaluated the current practice of pNEN surgery across Germany, including its adherence with guidelines and its perioperative outcomes.

Methods Patients who underwent surgery for pNENs (April 2013–June 2017) were retrieved from the prospective StuDoQ|Pancreas registry of the German Society of General and Visceral Surgery and retrospectively analyzed.

Results A total of 287 patients (53.7% male) with a mean age of 59.2 ± 14.2 years old underwent pancreatic resection for pNENs. Tumors were localized in the pancreatic head (40.4%), body (23%), or tail (36.6%). A total of 239 (83.3%) patients underwent formal resection with lymphadenectomy, 40 (14%) parenchyma-sparing resection, and 8 (2.8%) only exploration. Fifty (17.4%) patients underwent a minimally invasive approach. Among the 245 patients with complete pathological information, 42 (17.1%) had distant metastases, 78 (31.8%) had stage I tumors, 74 (30.2%) stage II, and 51 (20.8%) stage III. A total of 112 (45.7%) patients had G1 tumors, 101 (41.2%) G2, and 24 (9.8%) G3. Nodal involvement on imaging was an independent predictor of lymph node metastasis according to the multivariable analysis (odds ratio: 0.057; 95% confidence interval: 0.016–0.209; $p < 0.01$). R0 resection was reported in 240 (83.6%) patients. The 30- and 90-day mortality rates were 2.8% and 4.2%, respectively.

Conclusion In Germany the rate of potential curative resection for pNEN is high. However, formal pancreatic resection seems to be overrepresented, while minimally invasive resection is underrepresented.

Keywords Pancreatic neuroendocrine neoplasms · Surgery · Complication · StuDoQ|Pancreas registry

The members of For the StuDoQ|Pancreas study group of the German Society for General and Visceral Surgery (DGAV) are listed in Acknowledgements.

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Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are uncommon but fascinating tumors that present either as functional tumors, causing specific hormonal syndromes like organic hyperinsulinism, or as non-functional pNENs (NF-pNENs). They account for 2–4% of all clinically detected pancreatic tumors and thus represent an important subset of pancreatic neoplasms [1–3].

Because of advances in imaging modalities, NF-pNENs are diagnosed more frequently these days and now account for ≥ 70% of pNENs [4–6]. The natural history of pNENs is highly variable. While 90% of all insulinomas or small NF-pNENs (< 2 cm) are readily curable by surgical resection, most other functional and large NF-pNENs have a less favorable chance for a cure even with complete surgical resection, which should always be the major goal [7, 8]. Based on the current data, laparoscopic enucleation or distal pancreatic resection of insulinoma and small NF-pNENs is feasible and safe, so that current ENETS and German guidelines recommend a minimally invasive approach whenever technically feasible [7–9].

In localized tumors ≥ 2 cm in size, most experts advocate formal pancreatic resection with lymphadenectomy and, if necessary, resection of adjacent organs (stomach, colon, kidney, and adrenal gland) and/or major vascular resection [7]. The major goal is potentially curative R0 resection by either partial pancreatoduodenectomy or distal splenopancreatectomy with regional lymphadenectomy, depending on the localization of the tumor. In cases where a highly proliferative (Ki67 > 20%) G3 neuroendocrine carcinoma (NEC) is preoperatively diagnosed, several experts have advocated systemic chemotherapy over primary resection, since the risk of distant metastases is very high and the prognosis is extremely poor [9, 10].

In contrast, no data exist with respect to the positive effects of surgery on the overall survival in small (< 2 cm) NF-pNENs. Recent guidelines state that surveillance is a reasonable option for such small tumors, especially in elderly patients or patients with significant comorbidities [8]. Kümmerle and Rückert [11] reported the surgical strategies and perioperative outcomes of 282 patients with pNENs, including 207 with insulinomas, who underwent surgery in 16 university departments over the 10-year period between 1967 and 1976. For 70% of small pNENs, especially insulinomas, the favored procedures were enucleation and pancreatic tail resection. The perioperative mortality was 6.3%. A recent analysis of the StuDoQ|Pancreas registry regarding small pNENs (< 2 cm in size) showed that laparoscopic surgery is underrepresented in these tumors [12]. However, no further study has evaluated in detail the current clinical practice of pNEN surgery across Germany, including its indication, the types of procedures, or perioperative outcomes, as well as the adherence to current European and German guidelines.

We herein report on the basis of the nationwide StuDoQ|Pancreas registry of the German Society of General and Visceral Surgery the details of surgical treatments and the perioperative outcomes of patients with pNENs.

Methods

The German Society for General and Visceral Surgery (DGAV) established the DGAV StuDoQ, a nationwide registry for quality assessments in visceral surgery that has been prospectively maintained since September 2013 [13]. Data from participating centers are entered in a pseudonymized form at the institutional level without an over-institutional identifier in the prospective StuDoQ|Pancreas registry. All enrolled patients gave their written informed consent for data collection, and approval for data management has been obtained from the Technologie und Methodenplattform für die vernetzte medizinische Forschung (TMF) [14].

The main emphasis of the registry lies in the evaluation of the perioperative outcome for quality control. For the current analysis, patients who underwent pancreatic resection for pNENs were extracted from the StuDoQ|Pancreas registry. Data were extracted in anonymized form and analyzed for the demographics, tumor localization, type of surgical procedure, histology, and perioperative outcomes. The diagnosis of functional pNEN was based on the clinical and/or histopathological features, although due to the assembly of the registry, very rare functioning tumors, such as VIPoma, were not documented. TNM staging was determined according to the ENETS TNM staging system [15], and specimens were classified according to the WHO 2010 criteria [16]. The grading system proposed by the International Study Group of Pancreatic Fistula (ISGPF) [17] was used to classify postoperative pancreatic fistulas into grade A, B and C. Delayed gastric emptying (DGE) as well as postpancreatectomy hemorrhaging (PPH) were defined according to the proposed definitions of the International Study Group of Pancreatic Surgery (ISGPS) [18, 19]. Postoperative complications were classified according to the Clavien–Dindo classification system [20]. Details of the subgroup of patients with pNEN < 2 cm have already been reported [12].

Statistical analysis

Continuous variables are presented as mean values (standard deviation) and categorical variables as proportions. Quantitative variables were compared using Student's *t* test, and qualitative variables (e.g. gender) were compared using

the Chi square test or Fisher's exact test as appropriate. All reported probability values (p values) are based on two-sided tests, and the level of statistical significance was set at $p < 0.05$. Analyses were performed using the SPSS software program, ver. 23.0 (IBM Corp. Released 2015. IBM Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Binary logistic regression was performed to determine associations between preoperative variables and lymph node positivity. Factors that were significantly associated on a univariate analysis were included in the multivariable binary logistic regression model.

Results

Patient and tumor characteristics

Between April 2013 and April 2017, 287 (4.85%) of 5,918 patients enrolled in the StuDoQ|Pancreas registry underwent pancreatic resection for pNENs in 43 German surgical departments. Twenty-three (8%) patients had an insulinoma, while 264 (92%) had a non-functioning pNEN. Eighty-one (30.7%) of those with non-functional pNENs were symptomatic, whereas the remaining 183 (69.3%) tumors were incidentally discovered. The proportion of hereditary pNENs, such as multiple endocrine neoplasia type 1, could not be determined, since this was not documented in the registry. One hundred and fifty-four (53.7%) patients were male, and the mean age was 59.2 ± 14.2 years old. The mean body mass index (BMI) was 26.75 ± 5.3 kg/m^2. Of the 287 patients, 24 (8.4%) were classified as having an American Society of Anesthesiologists (ASA) physical status of I, 162 (56.4%) with II, and 101 (35.2%) with III. The baseline characteristics of the study population are shown in Table 1.

All tumors were preoperatively localized by imaging, and 161 (65.7%) of the 245 patients had tumors ≥ 2 cm in size. Preoperative imaging included computed tomography (CT) in 250 (87.1%), magnetic resonance imaging (MRI) in 122 (42.5%), and endoscopic ultrasonography (EUS) in 157 (54.7%) patients (Table 1). The use of somatostatin receptor imaging, such as Ga^{68}DOTATOC-positron emission tomography (PET)/CT, was not documented in the registry. The diagnosis of pNEN was established by the preoperative work-up in 153 (53.9%) patients, whereas the suspected preoperative diagnosis was malignant solid tumor in 119 (41.5%) and cystic pancreatic neoplasm in 15 (5.3%).

A preoperative EUS-guided biopsy/cytology was obtained in 97 (33.8%) of the 287 patients, confirming the diagnosis of pNEN in 77 (79.4%) patients. One hundred and sixteen (40.4%) pNENs were located in the pancreatic head, 66 (23%) in the body, and the remaining 105 (36.6%) in the tail. Based on the preoperative work-up, nodal involvement was suspected in 35 of 103 (34%) patients, and a radiological tumor size ≥ 2 cm was observed in 68 of 92 (73.9%) patients along with distant metastases in 49 (17%) of the 287 patients, primarily in the liver ($n = 37$, 75.5%) (Table 1).

Table 1 Baseline characteristics of resected patients

Variable	Mean (SD) or number of patients (n, %)
Patients (all)	287
Age (years)	59.2 ± 14.2
Sex (male)	154 (53.7%)
ASA I	24 (8.4%)
ASA II	162 (52.4%)
ASA III	101 (35.2%)
BMI (kg/m^2)	26.75 ± 5.3
Symptoms	
Abdominal pain	74 (25.8%)
Hypoglycaemia	23 (8%)
Jaundice	8 (2.8%)
Location	
Head	116 (40.4%)
Body	66 (23%)
Tail	105 (36.6%)
Preoperative imaging	
CT	250 (87.1%)
MRI	122 (42.5%)
EUS	157 (54.7%)
Preoperative tumor size > 2 cm on imaging	68/92 (73.9%)
Nodal involvement suspected by imaging	35/103 (34%)
Distal metastases suspected by imaging	49/287 (17%)
Patients with suspected liver metastases	37/287 (12.9%)

ASA American society of anesthesiologists, *BMI* body mass index, *CT* computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasonography, *SD* standard deviation

Surgical procedures and perioperative outcomes

Two hundred and thirty-nine (83.3%) patients underwent formal pancreatic resection with standard lymphadenectomy, including partial pancreatoduodenectomy in 89 (31%), distal pancreatectomy in 138 (48.1%) patients and total pancreatectomy in 12 (4.2%) (Table 2). Parenchyma-sparing resections were performed in 40 (14%) patients, including enucleation in 24 (8.4%) and other parenchyma-sparing resections, such as pancreatic tail resection or middle pancreatectomy, in 16 (5.6%). The remaining 8 (2.8%) patients underwent only surgical exploration. On comparing formal resections with parenchyma-sparing resections, no significant differences were noted in the patients' age (59.5 ± 13.9 vs. 57.1 ± 15.4 years, $p = 0.36$), BMI (26.9 ± 5.4 vs. 26.4 ± 5.2 kg/m^2, $p = 0.56$), ASA score

Table 2 Surgical procedures, postoperative outcomes, and pathological results of resected patients

Variable	Mean (SD) or number of patients (*n*, %)
Surgical procedures performed	287 (100%)
Formal pancreatic resections	239 (83.3%)
Whipple/PPPD	89 (31%)
Distal pancreatectomy	138 (48.1%)
Total pancreatectomy	12 (4.2%)
Parenchyma-sparing resections	40 (14%)
Enucleation	24 (8.4%)
Other parenchyma-sparing resections	16 (5.6%)
Surgical exploration only	8 (2.8%)
Open approach	237 (82.6%)
Minimally invasive approach (lap./lap.-assisted)	50 (17.4%)
Operation time (minutes)	265.3 ± 115
Clavien–Dindo (all)	161 (56.1%)
Clavien–Dindo I–II	80 (27.8%)
Clavien–Dindo III	61 (21.2%)
Clavien–Dindo IV	13 (4.5%)
Clavien–Dindo V	7 (2.4%)
POPF (all)	110 (38.3%)
Grade A	40 (13.9%)
Grade B	43 (15.0%)
Grade C	27 (9.4%)
DGE grade B/C	19 (6.6%)
PPH grade B/C	18 (6.3%)
LOS (days)	18.5 ± 13.7
R0 resection	240/287 (83.6%)
WHO 2010 grade[a]	
G1	112 (45.7%)
G2	101 (41.2%)
G3	24 (9.8%)
TNM staging	
T1 N0 M0	78/245 (31.8%)
T2 N0 M0	48/245 (19.6%)
T3 N0 M0	26/245 (10.6%)
T4 N0 M0	1/245 (0.4%)
Any T N1 M0	50/245 (20.4%)
Any T Any N M1	42/245 (17.1%)
Stage I	78 (31.8%)
Stage II	74 (30.2%)
Stage III	51 (20.8%)
Stage IV	42 (17.1%)

PPPD pylorus-preserving pancreaticoduodenectomy, *POPF* postoperative pancreatic fistula, *DGE* delayed gastric emptying, *PPH* postpancreatectomy haemorrhage, *LOS* length of hospital stay, *SD* standard deviation

[a]For 8 (3.3%) of 245 patients not documented

(I = 21, II = 131, III = 87 vs. I = 2, II = 28, III = 10, $p = 0.54$), or sex (male = 129, female = 110 vs. male = 18, female = 22, $p = 0.08$). On comparing the perioperative outcomes in the formal resection and parenchyma-sparing resection groups, the operating time was, as expected, significantly longer in the patients undergoing formal resection (275.07 ± 115.875 vs. 234.9 ± 94.03 min, $p = 0.02$). In accordance with the operative procedure performed, intraoperative transfusion of packed red blood cells was also significantly higher in patients undergoing formal resections than in those undergoing parenchyma-sparing resections (10% vs. 2.5%, $p = 0.01$). Rates of clinically relevant postoperative complications (Clavien–Dindo ≥ III) were comparable between the formal resection and parenchyma-sparing resection groups (29.3% vs. 25%, $p = 0.63$), with the rates of clinically relevant POPF in particular showing no significant differences between the groups (23.8% vs. 32.5%, $p = 0.86$). However, patients undergoing formal resections had a higher rate of postoperative pulmonary embolism than those undergoing parenchyma-sparing resections (2.5% vs. 0%, $p = 0.01$).

Major vascular resection (portal vein/coeliac trunk/SMA) was performed in only 8 (2.8%) patients. An open approach was applied in 237 (82.6%). Only 50 (17.4%) patients underwent a minimally invasive procedure, typically distal pancreatectomy (74%) (Table 2). However, the rate of minimally invasive procedures for pNENs was higher (17.4%) than for all other documented entities (6.2%) in the StuDoQlPancreas registry. Lymphadenectomy was performed in 239 (83.3%) of 287 patients. The median number of resected lymph nodes was 11 (range 0–46).

The overall mean operation time was 265.3 ± 115 min. The mean operation time in patients undergoing Whipple procedures or total pancreatectomy was significantly longer than in those undergoing distal pancreatectomy (351.08 ± 113.3 vs. 219.4 ± 81 min, $p < 0.001$). On comparing the open and minimally invasive approaches, no significant differences were found in patients undergoing distal pancreatectomy (217.04 ± 81.23 vs. 220.89 ± 80.86 min, $p = 0.8$) or enucleation (241.11 ± 80.37 vs. 194.00 ± 64.75 min, $p = 0.2$). Twenty-six (9.1%) of the 287 patients required intraoperative transfusion of packed red blood cells. In cases where adequate information was provided, a soft pancreas was reported in 161 (89.9%) of 179 patients, whereas a firm pancreas was only documented in 18 (10.1%) of 179 patients. A normal Wirsung duct diameter (< 3 mm) was reported in 106 (86.2%) of 123 patients, whereas 17 (13.8%) patients had a dilated (≥ 3 mm) Wirsung duct.

One hundred and sixty-one (56.1%) patients had postoperative complications, including 81 (28.1%) patients with clinically relevant complications (Clavien–Dindo grade ≥ III). The most frequent complication was clinically relevant (grade B or C) postoperative pancreatic fistula

(POPF), which occurred in 70 (24.4%) of 287 patients [grade B in 43 (15%) and grade C in 27 (9.4%); Table 2]. Distal pancreatectomy was significantly associated with higher rates of POPF than partial pancreatoduodenectomy (46.4% vs. 28.1%, $p=0.006$). There was no statistically significant difference in the rates of POPF when comparing the open and minimally invasive approaches ($p=0.24$; Table 3). Male sex was significantly associated with the occurrence of clinically relevant POPF in the present study cohort ($p=0.03$, Table 3). Delayed gastric emptying grade A, B, and C occurred in 24 (8.4%), 15 (5.2%) and 4 (1.4%) patients, respectively. PPH grade A was reported in 5 (1.7%) of 287 patients, grade B in 6 (2.1%) and grade C in 12 (4.2%). There was a trend towards statistical significance, when examining the association of POPF with the occurrence of PPH ($p=0.09$). Overall, in 45 of 287 patients (15.7%) reoperations were performed due to clinically relevant postoperative complications, including 27 patients with grade C POPF and 18 with postoperative bleeding.

The 30- and 90-day mortality rates were 2.8% and 4.2%. Major vascular resection was not significantly associated with increased mortality ($p=0.6$). The mean length of hospital stay was 18.5 ± 13.7 days and was significantly shorter in patients who underwent a minimally invasive approach than in those who received an open approach (13.4 ± 10.3 vs. 19.6 ± 14.1 days, $p=0.004$).

Pathological findings

Ninety-two (37.5%) of 245 patients with complete pathological information had malignant tumors with either lymph node and/or distant metastases. Of those, 51 (20.8%) and 42 (17.1%) patients had stage III and IV tumors with distant metastases, primarily in the liver (81%, $n=34/42$; Table 2). The remaining 152 (62%) patients had stage I ($n=78$, 31.8%) or stage II ($n=74$, 30.2%) tumors. One hundred and twelve (45.7%) patients had neuroendocrine tumor (NET) G1, 101 (41.2%) had NET G2, and 24 (9.8%) had NEC G3. In 8 cases (3.3%), the G status was not documented. R0 resection was achieved in 240 (83.6%) of 287 patients, including 34 (81.0%) of 42 patients with stage IV disease. Tumor grading was significantly associated with the presence of lymph node (G1 vs. G2 $p=0.01$; G1 vs. G3 $p<0.01$)

Table 4 Frequency of positive lymph nodes and distant metastases by each WHO grade

WHO grade	N0 (*n*, %)	N1 (*n*, %)	M0 (*n*, %)	M1 (*n*, %)
G1 ($n=112$)	90 (80.4%)	22 (19.6%)*	99 (88.4%)	13 (11.6%)$^{\neq}$
G2 ($n=101$)	61 (60.4%)	40 (39.6%)*	78 (77.2%)	23 (22.8%)$^{\neq}$
G3 ($n=24$)	10 (41.7%)	14 (58.3%)**	19 (79.2%)	5 (20.8%)

*G1 vs. G2, $p=0.01$

**G1 vs. G3 $p<0.01$

$^{\neq}$G1 vs. G2, $p=0.03$

Table 3 Results of the univariate analysis of factors associated with postoperative complications (Clavien–Dindo ≥ III) and POPF

Variables	Clavien–Dindo		*p value*	POPF		*p value*
	I–II ($n=80$)	≥ III ($n=81$)		Grade A ($n=40$)	Grade B/C ($n=70$)	
Age (years)	58 ± 16.3	60 ± 14	0.4	58 ± 17.1	58 ± 13.6	0.94
Sex (male)	41	50	0.2	18	46	0.03
BMI	26.2 ± 5.5	27.6 ± 5.2	0.09	26.6 ± 5.7	27.9 ± 6	0.27
ASA			0.93			
ASA I	3	8		4	6	0.49
ASA II	48	38		25	40	
ASA III	29	35		11	24	
Operation time (min)	266.9 ± 118.7	289.9 ± 119.5	0.22	241.8 ± 105.1	261.6 ± 99.7	0.33
Type of surgery			0.65			0.86
Formal resection	67	70		32	57	
Parenchyma-sparing resection	12	10		8	13	
Exploration only	1	1		–	–	
Surgical approach			0.49			0.24
Open	63	68		28	56	
Minimally invasive	16[a]	13		12	14	
LOS (days)	16 ± 6	30 ± 20	<0.001	18 ± 13.1	25 ± 16.6	0.02

BMI body mass index, *ASA* American society of anesthesiologists, *LOS* length of hospital stay, *POPF* postoperative pancreatic fistula

[a]For 1 patient not reported

and distant metastases (G1 vs. G2, $p = 0.03$), as shown in Table 4.

Based on the information provided by the registry, including patients' age, tumor localization, preoperative T and N status on imaging, and the presence of symptoms, predictors of positive lymph node metastases were determined. Preoperative grading was not included, since the majority of patients had not undergone a preoperative tumor biopsy. Tumor location in the pancreatic head [odds ratio (OR) 1.897; 95% confidence interval (CI) 1.096–3.282; $p = 0.02$] and lymph nodes detected on preoperative imaging (OR 0.062; 95% CI 0.018–0.215; $p < 0.01$) were identified as predictors of lymph node metastasis in the univariate analysis. Nodal involvement detected on preoperative imaging remained an independent predictor of lymph node metastasis in the multivariable analysis (OR 0.057; 95% CI 0.016–0.209; $p < 0.01$; Table 5).

Discussion

We herein report based on nationwide findings the indication and perioperative outcomes of surgery in 287 patients with pNENs in the German surgical community. In the present series the mean age at the diagnosis was 59.2 ± 14.2 years with a slight male predominance of 53.7%, which was similar to the median age of 56.4 years (range 14–93) and male proportion of 52% reported in the last study of the German NET registry [21]. The 92% rate of NF-pNENs in the present series was higher than in previous large-scale series with a reported prevalence ranging from 43.6 to 85% [4, 21–23]. This discrepancy can be explained by several reasons. First, in contrast to other studies, the present study enrolled all patients within 3 years. The widespread use of modern imaging in Germany may therefore have resulted in these tumors being detected more often than in previous studies. Second, several studies have suggested a rising incidence of NF-pNENs in the last decade [4–6]. Third, a few very rare functioning tumors might have been misclassified as NF-pNEN in the present study, due to the design of the database.

The preoperative assessment in the present series appeared somewhat suboptimal, as the diagnosis pNEN could preoperatively only be established in 53.9% of patients. In other series the preoperative diagnosis was confirmed in 63.7–85.2% of patients by preoperative work-up imaging [24, 25]. This discrepancy can be explained by the fact that not all available diagnostic tools, especially Ga^{68}DOTATOC-PET/CT and EUS, were used to confirm the diagnosis of pNEN preoperatively. For example, in the present study a preoperative EUS-guided biopsy/cytology was only obtained in 33% of patients.

In contrast to previous surgical series from the US and the Netherlands, which reported respective rates of 46% and 48% for stage IV disease in patients with pNENs [26, 27], the rate of stage IV disease in the present series was rather low at 17%. This is in line with the previous study from the Heidelberg group, which reported a rate of 20.3% [28]. This indicates good patient selection by participating hospitals, especially since the rate of R0 resection in cases of stage IV disease was 79%. This is also underscored by the fact that only 24 patients (9.8%) with NEC G3 underwent surgery, all without preoperative suspicion

Table 5 Predictors of LN metastases in patients with pancreatic neuroendocrine tumors

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age (years)						
≤60	1					
>60	0,755	0,439–1,300	0.311			
Tumor location						
Body/tail	1					
Head	1.897	1.096–3.282	0.02	2.831	0.976–8.209	0.05
Radiological tumor size (cm)						
≤2	1					
>2	1,511	0,379–6,023	0,56			
LN metastasis detected on imaging						
Yes	1					
No	0.062	0.018–0.215	<0.01	0.057	0.016–0.209	<0.01
Symptoms						
No	1					
Yes	1.272	0.717–2.256	0.411			

OR odds ratio, *CI* confidence interval, *LN* lymph node

of metastatic disease, which is in line with current ENETS and German guidelines [7, 9, 10].

In the present study the rate of formal resection with standard lymphadenectomy was as high as 83.3%, which included 78 of 245 patients with tumors < 2 cm in size on a pathological analysis. According to the current German guidelines and the recent ENETS consensus guidelines for the standard of care regarding surgery for pNENs [7–9], these latter patients should have been treated with parenchyma-sparing resection without lymphadenectomy. Thus, a proportion of patients with small G1 tumors were overtreated in the present study, as in other series [4, 22, 23, 26, 28, 29]. The 14% rate of parenchyma-sparing resection without standard lymphadenectomy in the present study falls within the range of rates reported in other retrospective series (12–17.7%) [4, 22, 23, 26]. One reason for the high rate of formal resection in patients with localized, non-metastatic pNENs might be the argument that parenchyma-sparing resection, especially enucleation, is associated with significantly higher complication rates than formal resection. However, Hüttner et al. [30] showed in a recent meta-analysis comparing surgical outcomes after enucleation versus standard resection for pancreatic neoplasms that enucleation can be performed with comparable safety in high-volume institutions and should therefore be considered instead of standard resection for selected pancreatic neoplasms. Similarly, in the present study, no significant differences were found when comparing the overall complication rates and clinically relevant POPF rates between patients who underwent formal and parenchyma-sparing resection. Another reason for the high rate of formal pancreatic resection might be oncological radicality. In the present study, the overall rate of R0 resection was 84%. These results are at the upper end of the range of reported in previous surgical series: 68–86.2% [4, 23, 28, 31]. Furthermore, when deciding on the most suitable surgical treatment, the risk of positive lymph nodes should be considered, since formal resection is usually combined with standard lymphadenectomy, whereas parenchyma-sparing resection, such as enucleation, is not. Therefore, the identification of predictors of lymph node metastases may help surgeons decide on the best course of surgical treatment with regard to patients' individual risk profiles.

In the present study nodal involvement detected on imaging was the only significant predictor of lymph node metastasis in the multivariable analysis. Partelli et al. [32] reported that nodal involvement detected on preoperative imaging and tumor size exceeding 4 cm were predictors of lymph node metastases in the multivariate analysis of a retrospective cohort of 181 patients with pNENs [32]. Other studies have similarly suggested tumor location in the pancreatic head, tumor size on imaging, and the presence of symptoms at the diagnosis as predictors of lymph node metastases in patients with pancreatic neuroendocrine tumors [33–35].

In addition, current German and ENETS Guidelines recommend a minimally invasive surgical approach, if technically feasible, in cases of preoperatively localized small pNENs [7–9]. In the present study, only 17% of patients underwent a minimally invasive procedure, suggesting that the use of minimally invasive surgery is underrepresented in the German surgical community. However, the present rates exceed previously reported rates in other large series from Europe, which ranged from 8 to 14.8% [4, 36]. The above-mentioned recommendation is based on a recent meta-analysis that concluded that laparoscopic pancreatic surgery resulted in a significantly shorter length of hospital stay, lower blood loss, and similar complication rates compared to open surgery [37]. The present study confirms these results, since the length of hospital stay was significantly shorter after minimally invasive surgery and the complication rate was not significantly different compared with the open approach. In the present study, 28% of patients had clinically relevant postoperative complications (Clavien–Dindo ≥ III), including 24.4% patients with clinically relevant POPF (Grade B/C). The 30- and 90-day mortality rates were 2.8% and 4.2%, respectively. These results are in the range of those reported in other large, contemporary series [22, 23, 28, 36, 38–41].

The present study has certain limitations that must be mentioned. First, the retrospective nature of the study must be taken into consideration. Second, the fact that the registry provides data only on resected patients precluded us from being able to compare surgical and non-surgical treatments during the same time period in the participating centers. Third, since very rare functioning tumors, such as VIPoma, were not documented due to the assembly of the registry, the rate of functioning pNENs might have been underreported. However, the present study enabled us to gain a realistic picture of the current surgical practice for pNENs in the German surgical community.

In conclusion, in Germany, the approach to patient selection for pNEN surgery seems to be acceptable, since the rate of potential curative resection is high. However, formal pancreatic resection seems to be overrepresented, while minimally invasive surgery is underrepresented.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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