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ORIGINAL ARTICLE

Indications and outcomes of enucleation versus formal pancreatectomy for pancreatic neuroendocrine tumors

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Abstract

Background: Pancreatoduodenectomy (PD) or distal pancreatectomy (DP) are common procedures for patients with a pancreatic neuroendocrine tumor (pNET). Nevertheless, certain patients may benefit from a pancreas-preserving resection such as enucleation (EN). The aim of this study was to define the indications and differences in long-term outcomes among patients undergoing EN and PD/DP.

Methods: Patients undergoing resection of a pNET between 1992 and 2016 were identified. Indications and outcomes were evaluated, and propensity score matching (PSM) analysis was performed to compare long-term outcomes between patients who underwent EN versus PD/DP.

Results: Among 1034 patients, 143 (13.8%) underwent EN, 304 (29.4%) PD, and 587 (56.8%) DP. Indications for EN were small size (1.5 cm, IQR:1.0–1.9), functional tumors (58.0%) that were mainly insulinomas (51.7%). After PSM (n = 109 per group), incidence of postoperative pancreatic fistula (POPF) grade B/C was higher after EN (24.5%) compared with PD/DP (14.0%) (p = 0.049). Median recurrence-free survival (RFS) was comparable among patients who underwent EN (47 months, 95% CI:23–71) versus PD/DP (37 months, 95% CI: 33–47, p = 0.480).

Conclusion: Comparable long-term outcomes were noted among patients who underwent EN versus PD/DP for pNET. The incidence of clinically significant POPF was higher after EN.

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Introduction

Pancreatic neuroendocrine tumors (pNETs) are relatively rare neoplasms with a markedly heterogeneous clinical behavior.[1] Although small size or low grade pNETs tend to display an indolent behavior with little tumor progression over time, large or high grade pNETs have stronger metastatic potential, thereby

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compromising long-term outcomes of patients.[2–4] Surgery remains the mainstay of treatment and the only option for cure among patients with pNETs. Traditional surgical approaches for patients with pNETs include pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) for tumors located at the head or the body/tail (i.e. left-side) of the pancreas, respectively. Due to the generally benign behavior of pNETs, the high morbidity rates, and long-term complications associated with pancreatic surgery, including life-long diabetes mellitus and exocrine pancreatic insufficiency, pancreas-preserving resections such as enucleation (EN) have been considered an attractive option in select patients with a pNET.[5–8]

Over the years, a better understanding of the biological behavior of pNETs has led to an expansion of the possible indications of EN for pNETs. In general, EN is reserved for very small pNET, patients with a genetic syndrome (i.e. MEN1), or patients with insulinomas located far from the pancreatic duct.[9–11] Proponents of EN include the preservation of healthy pancreatic parenchyma which, in turn, lowers the risk for post-operative pancreatic insufficiency. EN does not, however, involve resection of the tumor with a wide resection margin and lymphadenectomy is generally not performed at the time of EN, which could potentially compromise oncological outcomes.[12,13] To date, no clear recommendations exist around the indications regarding EN for pNETs. In addition, the majority of available studies report data from single center experiences or describe patients with a pNET as part of a larger study population, and, thus, the safety and efficacy of EN have not been thoroughly examined.[14–18] As such, the objective of the current study was to evaluate current surgical indications and complications of EN among patients with a pNET using a large multi-institutional database. In addition, this study examined long-term outcomes among patients undergoing a parenchymal-sparing procedure (i.e. EN) versus a formal pancreatic resection (i.e. DP or PD) for a pNET after adjusting for differences in baseline characteristics through a propensity score matching (PSM) analysis.

Materials and methods

Study population and inclusion criteria

Patients who underwent EN, PD, or DP for a pNET between 1992 and 2016 were retrospectively identified from 2 prospectively maintained multi-institutional databases. Patients underwent surgery in one of eight tertiary institutions comprising the United States Neuroendocrine Tumor Study Group (US-NETSG) (The Ohio State University Wexner Medical Center, Columbus, OH, USA; Virginia Mason Medical Center, Seattle, WA; Washington University School of Medicine, St Louis, Wisc, USA; University of Wisconsin School of Medicine and Public Health, Madison, Wisc, USA; Vanderbilt University, Nashville, TN, USA; Stanford University, Stanford, CA, USA; University of Michigan, Ann Arbor, MI, USA; Winship Cancer Institute, Emory University, Atlanta, GA, USA) or in one of two tertiary centers from the Netherlands (Erasmus Medical Center, Rotterdam, the Netherlands; Academic Medical Center, Amsterdam University Medical Centers, Amsterdam, The Netherlands). Patients who did not undergo curative-intent surgery, underwent R2 resection, underwent middle pancreatectomy, had metastases at time of surgery, and had missing follow-up were excluded. In 2016, both databases (US NETSG and Dutch) were reviewed and updated definitions (e.g. International Study Group on Pancreatic Surgery definitions[19]) were applied to all data, and pathological specimens were re-evaluated by experienced local pathologists. The study was approved by the Institutional Review Boards of all participating centers.

Variables of interest and definitions

Demographic and clinicopathological data included age, sex, body mass index (BMI), year of surgery, American Society of Anesthesiologists (ASA) score, comorbidities, presence of a genetic syndrome, functional tumor, symptomatic tumor, tumor size (on final pathology, in cm), tumor location (head, body, tail), multiple tumors, tumor grade, lymph node invasion, perineural invasion, resection margin, T, N, M stage, surgical approach, arterial or venous resection performed, operating time (minutes), and estimated blood loss (mL), length of hospital stay (days), time to surgery (i.e. time in days from date of tumor diagnosis on cross-sectional imaging until date of surgery), and development of recurrence (i.e. local or distant recurrence detected on cross-sectional imaging or confirmed through histopathology) and textbook outcome (TO). Specifically, TO was calculated and was defined as previously described (no severe post-operative complication, no 90-day mortality, no prolonged length-of-stay (LOS) (i.e. > 75th percentile), no 90-day readmission after discharge, and R0 resection).[20,21] Follow-up duration was defined as time from surgery until last clinical follow-up (or death).

Functional tumors were defined as lesions with hormonal overproduction combined with clinical symptoms (i.e. insulinoma, gastrinoma, glucagonoma, somatostatinoma and VIPoma). Tumor grade was determined according to the 2017 World Health Organization (WHO) Classification and updated in the current cohort.[22] Grade 1 tumors had a Ki-67 index of <3%, grade 2 tumors had a Ki-67 index of 3–20%, and grade 3 tumors had a Ki-67 index of >20%. Pathologic tumor T-, N-, and M-categories were defined according to the American Joint Committee on Cancer (AJCC) 8th edition manual.[23]

Post-operative complications within 90 days after surgery were recorded; severe post-operative complications were defined as Clavien-Dindo grade $\geq$3.[24] Post-operative pancreatic fistula (POPF) was defined according to the International Study Group for Pancreatic Fistula,[25] post-pancreatectomy hemorrhage and delayed gastric emptying were defined according to the International Study Group on Pancreatic Surgery.[19] An intra-abdominal abscess was defined as fluid collection detected on cross-sectional

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imaging combined with clinical symptoms. Other complications included deep surgical site infection (i.e. involving facial or muscle layers), post-operative pancreatitis (i.e. at least two of the following criteria: lipase/amylase level three times the upper limit of normal, abdominal pain suggestive for pancreatitis, abdominal imaging consistent with acute pancreatitis), pneumonia (i.e. requiring antibiotic treatment), reoperation (within 90 days), readmission (within 90 days), and death (within 90 days). An R0 resection was classified as a negative margin >1 mm, whereas a margin width ≤ 1 mm was categorized as R1.[26] Patients' follow-up included either ultrasound, abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) scanning at least once every year after surgery.

Statistical analysis

Descriptive statistics were presented as mean and standard deviation (±SD) for normally distributed variables, and median [interquartile range (IQR)] for non-normally distributed variables. Categorical variables were presented as frequency and percentages (%). In the unmatched cohort, the student's t-test or Mann–Whitney *U* test were used to compare continuous data and the X^2 test for categorical data. Differences in RFS were assessed using the Kaplan–Meier method and the log-rank test. The 5-year RFS rate was calculated using the Kaplan Meier method.

To adjust for potential confounding factors, a PSM analysis was performed among patients who underwent EN versus formal pancreatic resection (i.e. PD or DP). Logistic regression analysis was performed to estimate propensity score using nearest neighbor matching. The ratio for matching was established at a 1:1 ratio with a caliper width equal to 0.1.[27] Propensity score matching was performed taking into account known confounding factors in the allocation of patients of patients to EN, PD, or DP. The outcome of interest was recurrence, and whether patients who underwent EN had lower recurrence rates compared with patients who had more extensive resection performed (i.e. PD, DP). These confounding factors included: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, presence of a genetic syndrome (yes, no), functional tumor (yes, no), tumor location (head, body, tail), and tumor size (continuous). Patients with missing covariates necessary for the propensity score matching were automatically excluded by the program *R*. Standardized differences and P-values were used to compare characteristics between the matched and unmatched groups. A standardized difference of less than 0.2 was considered to reflect adequate balance. In the matched cohort, paired analyses were used, where continuous data was compared using the paired t-test or Wilcoxon Signed Rank test and categorical data using the McNemar test. All analyses were performed using SPSS v 23.0 (IBM, Inc, Armonk, NY) and R version 3.4.3 (cran.r-project.org). Statistical significance was assessed at $\alpha = 0.05$ (two-tailed).

Results

Patient and tumor characteristics

A total of 1034 patients underwent resection for a pNET and were included in the final cohort (Table 1). Of note, patients who underwent EN less frequently had diabetes, hypertension, and MEN1 syndrome compared with individuals who underwent PD or DP. In addition, patients who underwent EN more frequently had grade 1, functional tumors and smaller size tumors. On pathology, EN patients more frequently had T1 tumors while the incidence of an R0 resection was lower, however, among patients who underwent EN compared with PD or DP.

Perioperative and postoperative outcomes

Postoperative outcomes after EN, PD, and DP are summarized in Table 2. The majority of patients underwent an open procedure (EN: n = 112, 78.3% vs. PD: n = 301, 99.0% vs. DP: n = 347, 59.1%, p < 0.001). Among DP patients, up to 71.1% (n = 421) had a concomitant splenectomy. Arterial resections on the other hand were rarely performed, and major venous resection was performed mainly during PD (n = 22, 9.2%) followed by DP (n = 9, 1.8%), but never during EN (p < 0.001). Not surprisingly, median operative time was shorter for EN (190 min, IQR 156–228) compared with PD (338 min, IQR 265–441) or DP (216 min, IQR 180–279) (p < 0.001). In addition, EN was associated with lower estimated blood loss (10 mL, IQR 0–125) compared with DP (150 mL, IQR 50–350) and PD (300 mL, IQR 150–525) (p < 0.001) (Table 2).

In the unmatched cohort, not surprisingly, PD was associated with higher rates of severe complications (Clavien-Dindo grade ≥3) (PD: n = 98, 32.2% vs. DP: n = 114, 19.5% vs. EN: n = 36, 25.4%, p = 0.001), intra-abdominal abscess grade B/C (PD: n = 46, 15.4% vs. DP: n = 58, 10.4% vs. EN: n = 10, 7.1%, p = 0.020), delayed gastric emptying grade B/C (PD: n = 37, 12.4% vs. DP: n = 31, 5.5% vs. EN: n = 14, 10.0%, p = 0.002), and lower rates of textbook outcomes (PD: 35.5% vs DP: 57.6% vs EN: 46.7%, p<0.001) compared with DP and EN (Table 2).

To minimize potential confounding, PSM was utilized to create two matched cohorts of 109 patients (Supplemental Table 1). Of note, following PSM, EN was associated with lower median operative time (EN: 190 min, IQR 154–200 vs. PD/DP: 254 min, IQR 200–334, p < 0.001) and lower estimated blood loss compared with a formal resection (EN: 100 mL, IQR 10–200 vs. PD/DP: 250 mL, IQR 100–500, p = 0.021. No differences were noted in the incidence of severe complications. In contrast, patients who underwent EN had higher rates of POPF grade B/C (n = 26, 24.5%) compared with individuals who underwent DP/PD (n = 15, 14.0%, p = 0.049) (Table 2, Supplemental Table 2). Despite higher rates of POPF among EN patients, textbook outcome rates were comparable (Table 2).

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Table 1 Patient and tumor characteristics

	All patients (n = 1034)	EN (n = 143)	PD (n = 304)	DP (n = 587)	*P*
Patient					
Male, %	524 (50.7)	65 (45.5)	146 (48.0)	313 (53.3)	0.131
Age, ± SD	56(13.6)	54(14.7)	56 (13.3)	56 (13.5)	0.205
BMI, ± SD	28.6 (6.6)	27.6 (5.8)	27.6 (6.4)	29.4 (13.5)	**<0.001**
Year of Surgery					
1992–1999	32 (3.1)	8 (5.6)	9 (3.0)	15(2.6)	**0.004**
2000–2005	111 (10.7)	27 (18.9)	36 (11.8)	48 (8.2)	
2006–2010	363 (35.1)	45 (31.5)	110 (36.2)	208 (35.4)	
2011–2016	528 (51.1)	63 (44.1)	149 (49.0)	316 (53.8)	
ASA, %					
I	85 (8.2)	21 (14.7)	24 (7.9)	40 (6.8)	0.056
II	484 (46.8)	67 (46.9)	145 (47.7)	272 (46.3)	
III	449 (43.4)	52 (36.4)	129 (42.4)	268 (45.7)	
IV	16 (1.5)	3 (2.1)	6 (2.0)	7 (1.2)	
Comorbidities, %					
Diabetes	198 (19.2)	8 (5.6)	57 (18.8)	133 (22.7)	**<0.001**
Pulmonary	27 (2.6)	3 (2.1)	11 (3.6)	13 (2.2)	0.522
Hypertension	419 (40.6)	43 (30.1)	125 (41.1)	251 (43.0)	**0.019**
Cardiac	114 (11.1)	21 (14.9)	30 (9.9)	63 (10.8)	0.391
Other malignancy	66 (6.4)	8 (5.6)	1 (5.9)	40 (6.8)	0.799
Previous abdominal surgery	61 (5.9)	17 (29.3)	18 (28.6)	26 (34.7)	0.421
Genetic syndrome					
No	938 (90.7)	135 (94.4)	278 (91.4)	525 (89.4)	**0.031**
MEN1	80 (7.7)	7 (4.9)	18 (5.9)	55 (9.4)	
Other	16 (1.6)	1 (0.7)	8 (2.6)	8 (1.2)	
Tumor					
Functional tumor, %					
No	834 (80.7)	60 (42.0)	277 (91.1)	497 (84.7)	**0.001**
Yes	200 (19.3)	83 (58.0)	28 (9.2)	87 (14.8)	
Insulinoma	151 (14.6)	74 (51.7)	13 (4.3)	64 (10.9)	
Glucagonoma	5 (3.5)	1 (0.7)	2 (0.7)	2 (0.3)	
Gastrinoma	35 (24.5)	8 (5.6)	11 (3.6)	16 (2.7)	
VIPoma	6 (4.2)	0	2 (0.7)	4 (0.7)	
Somatostatinoma	1 (0.7)	0	0	1 (0.2)	
Tumor size, IQR, cm	2.1 (1.3–3.5)	1.5 (1.0–1.9)	2.8 (1.7–4.0)	2.0 (1.3–3.6)	**<0.001**
Tumor location, %					
Head	344 (33.3)	73 (51.0)	271 (89.1)	0	**N/A**
Body	261 (25.2)	48 (33.6)	32 (10.5)	181 (30.8)	
Tail	429 (41.5)	22 (15.4)	1 (0.3)	406 (69.2)	
Multiple tumors, %	35 (4.2)	1 (1.2)	9 (3.7)	25 (4.9)	0.260
Pathological					
Tumor Grade, %					
G1	565 (66.2)	97 (85.1)	138 (55.0)	330 (67.6)	**<0.001**
G2	255 (29.9)	17 (14.9)	91 (36.3)	147 (30.1)	

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Table 1 (*continued*)

Patient	All patients (n = 1034)	EN (n = 143)	PD (n = 304)	DP (n = 587)	*P*
G3	33 (3.9)	0	22 (8.8)	11 (2.3)	
LVI, %	208 (29.1)	6 (9.2)	88 (41.9)	114 (25.9)	**<0.001**
PNI, %	137 (20.9)	0	73 (24.0)	64 (10.9)	**<0.001**
Resection Margin, %					
R0	818 (79.1)	92 (72.4)	261 (86.1)	497 (85.1)	**0.012**
R1	216 (20.9)	35 (27.6)	42 (13.9)	87 (14.9)	
T stage, %					
T1	429 (47.0)	88 (79.3)	75 (28.5)	266 (49.4)	**<0.001**
T2	290 (31.8)	18 (16.2)	90 (34.2)	182 (33.8)	
T3	188 (20.6)	4 (3.6)	96 (36.5)	88 (16.3)	
T4	3 (0.3)	0	2 (0.8)	1 (0.2)	
N stage, %					
Nx	116 (12.7)	58 (52.3)	8 (3.0)	50 (9.3)	**<0.001**
N0	603 (66.0)	46 (41.1)	154 (58.3)	403 (74.8)	
N1	195 (21.3)	7 (6.3)	102 (38.6)	86 (16.0)	

EN, enucleation; PD, pancreatoduodenectomy; DP, distal pancreatectomy; BMI, body mass index; ASA, American Association of Anesthesiologists classification; MEN, Multiple Endocrine Neoplasia syndrome; LVI, lymph node invasion; PNI, perineural invasion.
Bold values denote statistical significance.

Long-term outcomes

After a median follow-up of 42 months (95% CI 27–57), median and 5-year RFS following EN (n = 109) or PD/DP (n = 865) was 32 (95% CI 21–43) months and 82.2% versus 45.8 (95% CI 20–72) months and 75.7% in the unmatched cohort, respectively (p = 0.12, Fig. 1). In the PSM cohort (n = 109 in each group), median and 5-year RFS remained comparable following EN (median: 47 months, 95% CI 23–71; 5-year RFS: 83.0%) or PD/DP (median: 37 months, 95% CI 33–47; 5-year RFS: 75.5%, p = 0.480, Fig. 2). In the PSM cohort, a total of 9 (9.7%) and 12 (12.0%) patients experienced a recurrence in the EN and PD/DP groups respectively, while only 1 patient (1.1%) died within 90 after EN (Table 2).

Discussion

Traditional surgical approaches for pNETs include a standard pancreatic resection (i.e. PD, DP), yet morbidity rates still can be as high as 40–50%.[3,28] Rather than standard pancreatectomy, EN has been suggested to be an option for some patients with pNET. There are concerns, however, whether EN is an oncological sound procedure since limited pancreatic tissue is resected and lymph nodes are rarely evaluated during this procedure. The current study was important because both short- and long-term outcomes were evaluated following EN versus PD and DP among patients with pNETs using a large, multi-institutional database. Of note, the majority of patients who underwent EN had a small size pNET (mean: 1.7 cm), with insulinomas (51.7%) being the most prevalent indication for EN. When examining post-operative complications, a POPF grade B/C occurred more frequently after EN compared with standard pancreatic resection (PD/DP) (24.5% vs. 14.0%, p = 0.049). In contrast, 5-year RFS was comparable among patients who underwent EN versus PD/DP (83.0% vs. 75.5%, p = 0.480).

Proponents of EN have noted that this approach preserves healthy pancreatic parenchyma, which can minimize the risk of endocrine and exocrine pancreatic insufficiency, as well as improve long-term functional outcomes compared with standard pancreatic resections (i.e. PD, DP).[7,29] EN has been reported to be safe and effective for the treatment of insulinomas or non-functional tumors with a diameter of less than 4 cm and benign biological behavior.[9,30–32] Nevertheless, due to the lack of clear recommendations, it is typically up to the discretion of the surgeon whether patients with pNETs are treated with a parenchyma-preserving procedure (i.e. EN) or a formal pancreatectomy (i.e. PD, DP). In the current study, the majority of patients who underwent EN had a small size pNET (mean: 1.7 cm), with insulinomas (51.7%) and functional tumors (58.0%) being the most prevalent indication. This finding was consistent with previous studies that reported functional tumors as the most common indication for EN.[30,33] In addition, most enucleated pNETs were located in the head of the pancreas (51.0%). The reason for the higher utilization of EN for head lesions is likely multi-factorial and may be related to the higher anticipated morbidity and mortality associated with standard PD

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Table 2 Peri and post-operative outcomes after surgery for a pNET

	Before matching				After matching		
	EN (n = 143)	PD (n = 304)	DP (n = 587)	*P*	EN (n = 109)	PD/DP (n = 109)	*P*
Perioperative Outcomes							
Surgical Approach, %							
Open	112 (78.3)	301 (99.0)	347 (59.1)	**<0.001**	85 (78.0)	78 (71.6)	0.275
Minimally invasive	31 (21.7)	3 (1.0)	240 (40.9)		24 (22.0)	31 (28.4)	
Splenectomy	NA	NA	427 (71.7)	N/A	NA	35 (16.1)	N/A
Arterial resection, %	0	1 (0.4)	1 (0.2)	0.759	0	0	1.00
Venous resection, %	0	22 (9.2)	9 (1.8)	**<0.001**	0	0	1.00
Operating time, IQR, min	190 (156–228)	338 (265–441)	216 (180–279)	**<0.001**	190 (154–220)	254 (200–334)	**<0.01**
Estimated blood loss, IQR, mL	10 (0–125)	300 (150–525)	150 (50–350)	**<0.001**	100 (10–200)	250 (100–500)	**0.021**
Postoperative Outcomes							
Complications Clavien-Dindo grade 3, %	36 (25.4)	98 (32.2)	114 (19.5)	**0.001**	28 (34.6)	31 (31.6)	0.559
Deep surgical site infection, %	6 (4.3)	17 (5.7)	28 (5.0)	0.827	1 (1.0)	4 (3.7)	0.185
Post-operative pancreatitis, %	1 (0.8)	1 (0.4)	7 (1.2)	0.397	1 (1.0)	1 (1.0)	1.00
Pneumonia, %	4 (2.9)	9 (3.0)	23 (4.1)	0.626	3 (2.8)	7 (6.5)	0.200
POPF grade B/C, %	46 (32.9)	68 (22.7)	161 (28.7)	0.055	26 (24.5)	15 (14.0)	**0.049**
PPH grade B/C, %	5 (3.6)	19 (6.4)	17 (3.0)	0.062	3 (2.8)	4 (3.7)	0.710
Intra-abdominal abscess grade B/C, %	10 (7.1)	46 (15.4)	58 (10.4)	**0.020**	7 (6.6)	11 (10.3)	0.335
Delayed gastric emptying grade B/C, %	14 (10.0)	37 (12.4)	31 (5.5)	**0.002**	10 (9.4)	15 (14.0)	0.299
Length of hospital stay, IQR, days	8 (5–11)	9 (7–15)	6 (5–9)	**0.005**	8 (5–11)	8 (6–12)	0.214
Reoperation, %	8 (5.7)	18 (6.0)	26 (4.6)	0.655	6 (5.7)	4 (3.7)	0.507
Readmission <90 days, %	19 (13.4)	77 (25.4)	106 (18.2)	**0.030**	13 (14.1)	15 (14.4)	0.731
Death, <90 days %	2 (1.4)	6 (2.0)	8 (1.4)	0.771	1 (1.1)	0 (0)	0.323
Textbook outcome, %	63 (46.7)	108 (35.5)	336 (57.6)	**<0.001**	48 (45.2)	51 (49.0)	0.944
Long-term outcomes							
Recurrence, %	10 (7.0)	75 (24.7)	81 (13.8)	**<0.001**	9 (9.7)	12 (12.0)	0.610

EN, enucleation; PD, pancreatoduodenectomy; DP, distal pancreatectomy; POPF, post-operative pancreatic fistula; PPH, post-pancreatectomy hemorrhage.
Bold values denote statistical significance.

which is weighted against treating a relatively benign neoplasm with a more preservative approach (i.e. EN). In contrast, DP is a procedure with lower morbidity and thus tumors in the pancreatic tail are less likely to be treated with EN.[34]

Despite the potential advantages of EN over standard pancreatic resections, EN may lead to higher rates of clinically relevant POPF,[8,15] which occur more frequently when EN is performed for pNETs compared with other neoplasms.[8,35] While POPF can arise from either the pancreaticojejunostomy or pancreaticogastrostomy anastomosis after PD procedures, in EN POPF can originate directly from the pancreatic tissue and duct.[34] To this point, patients in the current study who underwent EN had nearly a two-fold higher incidence of grade B/C POPF following EN (24.5%) compared with PD/DP (14.0%) for pNET (Table 2). Although the reason for higher POPF rates after EN may be multifactorial, Brient et al. demonstrated that distance of the lesion from the pancreatic duct of <2 mm was the most important factor associated with the development of POPF.[36] In addition, previous investigators have suggested that pNETs are associated with less inflammation and stromal changes in the pancreatic parenchyma compared with other pancreatic lesions, which leads to a soft and friable pancreas during surgery and, in turn, higher rates of pancreatic fistula after resection.[37]

Obtaining optimal oncological outcomes with EN for pNETs has been debated. In the current study, while patients who underwent PD or DP were more likely to have a negative surgical margin and more lymph nodes evaluated than patients who had EN, these differences did not translate into long-term benefits. Specifically, there was no difference in RFS among patients who underwent EN versus more extensive pancreatic resection such as PD or DP for pNET in both the unmatched and the PSM cohorts. These data are consistent with previous studies that reported

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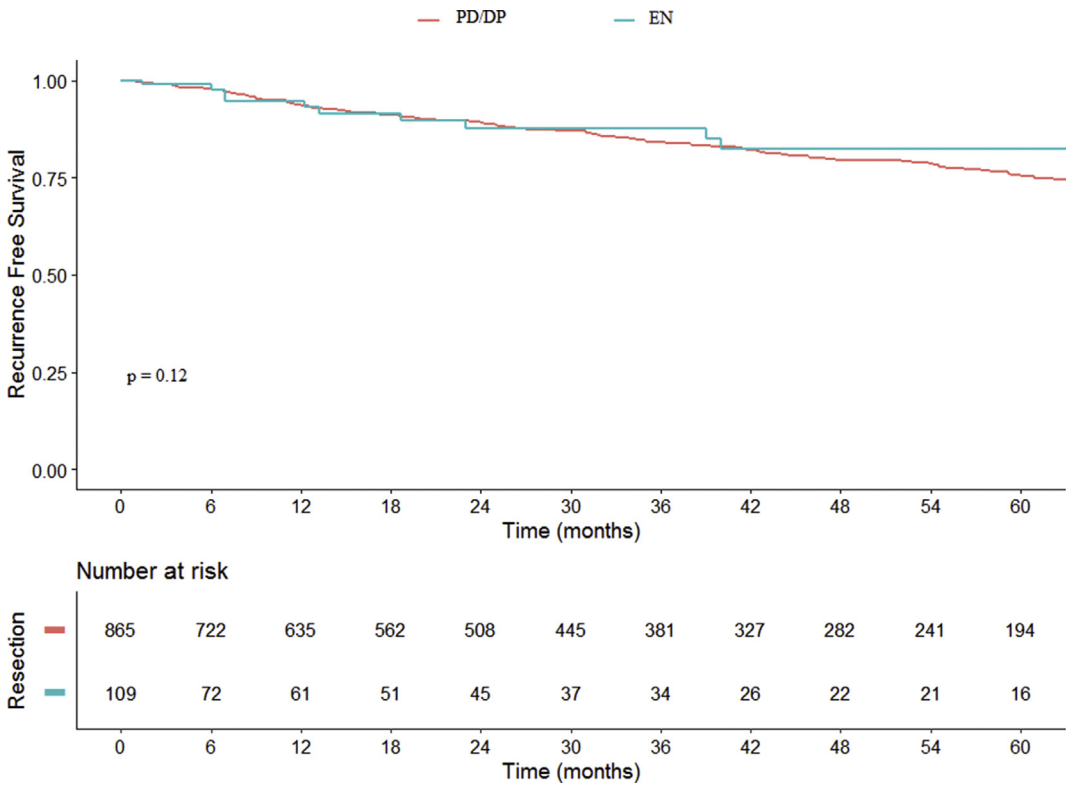

Figure 1 Kaplan–Meier curves demonstrating differences in RFS among patients with pNET who underwent EN versus PD/DP in the unmatched cohort

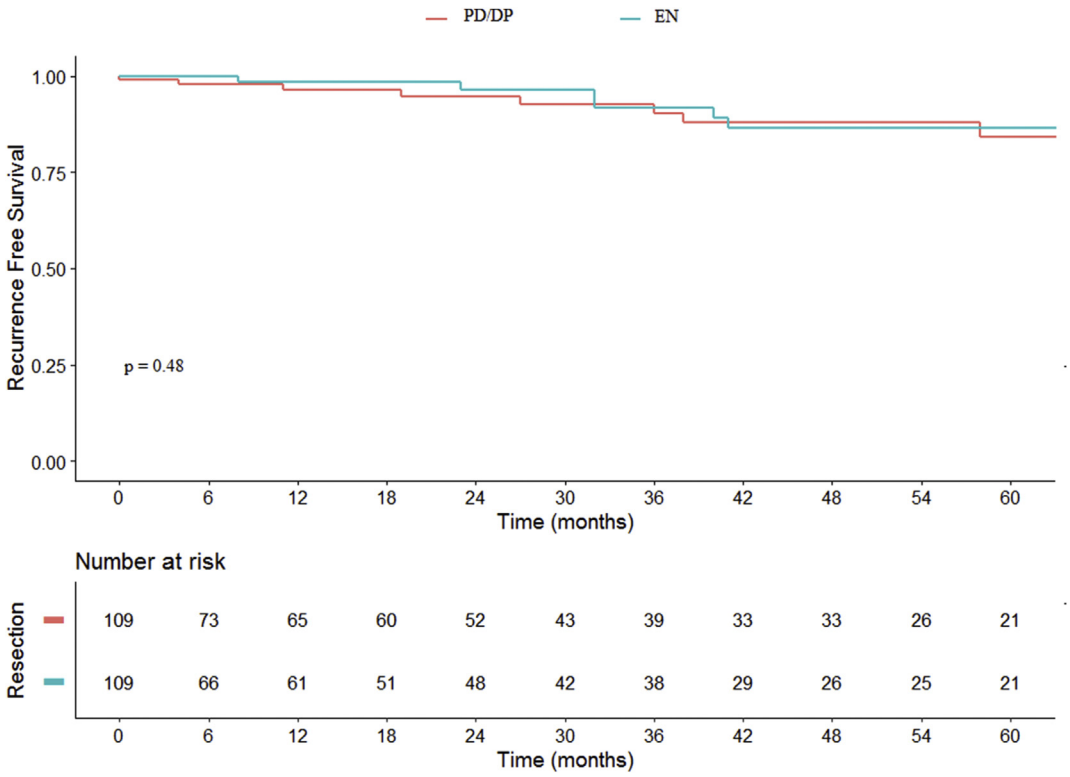

Figure 2 Kaplan–Meier curves demonstrating differences in RFS among patients with pNET who underwent EN versus PD/DP in the propensity score matched cohort

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comparable long-term outcomes after EN versus regular pancreatectomy among patients with small pNETs.[9,30] Whether EN can be utilized for larger pNETs while maintaining comparable results has been debated, with some investigators arguing that EN should be only considered among patients with pNETs <2 cm.[10,38,39] In the current study the median tumor size among patients with EN was 1.5 cm (IQR 1.0–1.9). Collectively, the data suggest that EN may be associated with similar long-term outcomes compared with standard pancreatectomy among appropriately selected patients with pNETs.

There are several limitations that should be considered when interpreting the results. As with all retrospective studies, the current study was subject to selection bias. The decision to perform EN versus standard pancreatectomy (PD or DP) in patients with a pNET was at the discretion of the treating surgeon, patient preference, and local practice. In addition, information on distance of the tumor from the pancreatic duct was not available in order to assess this factor relative to POPF risk. Information on quality of life after EN, DP, PD was also not available. In addition, differences in surgical techniques, and perioperative management of patients at different participating institutions may have influenced the short-term outcomes of patients. Although PSM reduced bias secondary to confounding, PSM cannot fully adjust for all unmeasured confounders that may have been present in the EN, PD and DP groups, such as hospital and surgeon characteristics. In addition, while PD and DP are different procedures with different morbidity and mortality, these operations are considerably more extensive compared with EN and, thus, were treated as one group ("standard pancreatic resections") for the purposes of the PSM analysis.

In conclusion, based on data from a large multi-institutional cohort, the main indications for EN were small, functional pNETs that were predominantly insulinomas. Although comparable long-term oncologic outcomes were noted among patients who underwent EN versus standard pancreatectomy (i.e. PD, DP), the incidence of clinically significant POPF was higher after EN.

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Conflict of interest
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.06.015.

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