Xu-Feng Zhang ORCID iD: 0000-0002-4483-7326

Bradley Krasnick ORCID iD: 0000-0003-2685-7259

Timothy Pawlik ORCID iD: 0000-0002-4828-8096

Minimally Invasive versus Open Distal Pancreatectomy for Pancreatic Neuroendocrine Tumors: An Analysis from the U.S. Neuroendocrine Tumor Study Group

Authors: Xu-Feng Zhang MD, PhD[1,2]; Alexandra G. Lopez-Aguiar MD[3]; George Poultsides MD[4]; Eleftherios Makris MD[4]; Flavio Rocha MD[5]; Zaheer Kanji MD[5]; Sharon Weber MD[6]; Ryan Fields MD[7]; Bradley A. Krasnick MD[7]; Kamran Idrees MD[8]; Paula M. Smith MD[8]; Cliff Cho MD[9]; Carl R. Schmidt MD[2]; Shishir K Maithel MD[3]; Timothy M. Pawlik MD, MPH, PhD[2], and The United States Neuroendocrine Tumor Study Group

Affiliations:

[1] Department of Hepatobiliary Surgery and Institute of Advanced Surgical Technology and Engineering, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

[2] Department of Surgery, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio

[3] Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, Georgia

[4] Department of Surgery, Stanford University, Palo Alto, California

[5] Department of Surgery, Virginia Mason Medical Center, Seattle, Washington

[6] Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

[7] Department of Surgery, Washington University School of Medicine, St. Louis, Wisconsin

[8] Division of Surgical Oncology, Department of Surgery, Vanderbilt University, Nashville, Tennessee

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[9] Division of Hepatopancreatobiliary and Advanced Gastrointestinal Surgery, Department of Surgery, University of Michigan, Ann Arbor, Michigan

Corresponding Author:

Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.)

Professor and Chair, Department of Surgery

The Urban Meyer III and Shelley Meyer Chair for Cancer Research

Professor of Surgery, Oncology, Health Services Management and Policy

The Ohio State University, Wexner Medical Center

395 W. 12th Ave., Suite 670

614 293 8701 phone

614 293 4063 fax

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Author contributions: Conception and design, acquisition of data, and analysis and interpretation of data, manuscript writing: Xu-Feng Zhang, Yi Lv, Timothy M Pawlik; Acquisition and interpretation of the data: Alexandra G. Lopez-Aguiar, George Poultsides, Eleftherios Makris, Flavio Rocha, Zaheer Kanji, Sharon Weber, Alexander Fisher, Ryan Fields, Bradley A. Krasnick, Kamran Idrees, Paula M. Smith, Cliff Cho, Megan Beems; Conception and design, analysis and interpretation of data, and revising the article: Carl R. Schmidt, Mary Dillhoff, Shishir K Maithel, Timothy M Pawlik

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Synopsis for Table of Contents: Minimally invasive distal pancreatectomy (MIDP) was increasingly performed versus open distal pancreatectomy (ODP) for pancreatic neuroendocrine tumors (pNETs). Patients who underwent MIDP had less blood loss, lower incidence of severe complication, and a shorter hospital stay versus ODP. Patients

undergoing MIDP over ODP in treatment of pNET had comparable oncologic surgical metrics, as well as similar long-term OS.

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Abstract

Background: To determine short- and long-term oncologic outcomes after minimally invasive distal pancreatectomy (MIDP) with open distal pancreatectomy (ODP) for treatment of pancreatic neuroendocrine tumor (pNET).

Methods: Data of the patients who underwent curative MIDP or ODP for pNET between 2000 and 2016 were collected from a multi-institutional database. Propensity score matching (PSM) was used to generate 1:1 matched MIDP and ODP patients.

Results: A total of 576 patients undergoing curative DP for pNET were included. 214 (37.2%) patients underwent MIDP, whereas 362 (62.8%) underwent ODP. MIDP was increasingly performed over time (2000-2004: 9.3% vs. 2013-2016: 54.8%; $p<0.01$). In the matched cohort (n=141 in each group), patients who underwent MIDP had less blood loss (median, 100 vs. 200 ml, $p<0.001$), lower incidence of Clavien-Dindo ≥ III complications (12.1% vs. 24.8%, $p=0.026$), and a shorter hospital stay versus ODP (median, 4 versus 7 days, $p=0.026$). Patients who underwent MIDP had a lower incidence of recurrence (5-year cumulative recurrence, 10.1% vs. 31.1%, $p<0.001$), yet equivalent overall survival rate (5-year OS, 92.1% vs. 90.9%, $p=0.550$) compared with patients who underwent OPD.

Conclusion: Patients undergoing MIDP over ODP in treatment of pNET had comparable oncologic surgical metrics, as well as similar long-term OS.

Key words: laparoscopic; robotic; neuroendocrine tumor; pancreas; prognosis

Introduction

Pancreatic neuroendocrine tumors (pNET) account for 2% to 4% of all pancreatic neoplasms diagnosed in the general population.[1,2] Over the last two decades, the incidence of pNET has increased significantly due to the widespread use of cross-sectional imaging.[3] In fact, the incidence of pNET currently is about 0.48 per 100,000 persons and pNET is the leading cause of cancer related deaths in the United States.[4,5] Although most cases are sporadic, 10%-30% are associated with genetic syndromes, such as multiple endocrine neoplasia (MEN) 1 syndrome, and Von Hippel-Lindau (VHL) disease.[1,2]

Surgical resection remains the optimal curative modality for pNET and is the treatment of choice even among certain patients with locally advanced or metastatic disease.[6-9] The surgical approach can consist of “typical” and “atypical” resections depending on the number, size and location of the tumor(s). Typical resection includes pancreaticoduodenectomy (PD) for tumors located in the pancreatic head, distal pancreatectomy (DP) for tumors located in the body and tail, and rarely total pancreatectomy (TP) when tumors spread within the whole gland.[3,10] Atypical resection includes enucleation and central pancreatectomy and is more often utilized when tumors are small (<2-3 cm), benign, well-circumscribed, as well as not adjacent to the duct of Wirsung so that the duct can remain intact after tumor resection.[10,11]

Since the first laparoscopic pancreatic surgery performed by Coushieri in 1994,[12] laparoscopic surgery has been increasingly utilized in pancreatic surgery due to its minimal invasiveness versus open procedures.[3,13-16] Due to its overall relatively low incidence, the assessment of short- and long-term outcomes following laparoscopic

versus open surgery for pNET have been limited. Especially, most data have been derived from small retrospective studies that have yielded disparate results.[3,10,15,16] In addition, the heterogeneity of patients who had different tumor locations requiring different surgical procedures may induce selection bias when comparing minimally invasive versus open surgical approaches. In addition, most previous studies largely focused on short-term outcomes with the long-term oncological outcomes of minimally invasive versus open surgery for pNETs remaining largely undetermined.[10] Therefore, the objective of the current study was to define short- and long-term outcomes following minimally invasive distal pancreatectomy (MIDP) versus open distal pancreatectomy (ODP) among patients with pNETs located in the body and tail of the pancreas.

Patients and methods

Design and patients

Patients who underwent curative resection for pNET between 2000 and 2016 were identified from the U.S. Neuroendocrine Tumor Study Group (US-NETSG). The US-NETSG included The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, OH; Winship Cancer Institute, Emory University, Atlanta, GA; Stanford University, Palo Alto, CA; Virginia Mason Medical Center, Seattle, WA; University of Wisconsin, School of Medicine and Public Health, Madison, WI; Washington University, School of Medicine, St. Louis, MO; Vanderbilt University, Nashville, TN; University of Michigan, Ann Arbor, MI.[17] The Institutional Review Board of each participating institution approved the study.

All patients were pathologically diagnosed with pNET based on conventional histology and immunohistochemical findings (chromogranin A, synaptophysin and Ki 67). Standard patient demographic, clinicopathologic and perioperative data were collected based on a prospectively maintained database.

Surgical treatment and postoperative surveillance

All surgeries were performed by specialized physicians. Choice of laparoscopic/robotic or open surgery was mostly determined by tumor factors, as well as surgeon preference. Operative time was defined as the time duration between the first incision and skin closure. Margin status was determined by the pathologist based on examination of all specimen margin sites on permanent sections. An R0 resection was defined as a minimum margin length of > 1mm; the microscopic presence of tumor at the margin or a minimum margin length of ≤ 1 mm was designated as an R1 resection. The inability to resect all gross residual disease was defined as an R2 resection.[18] Tumor-related characteristics, including maximal tumor diameter, number, location, tumor morphology, histological grade, lymph-vascular/perineural invasion, Ki-67, mitotic rate, nodal status were recorded based on final pathology. All cases were reviewed and classified according to the World Health Organization (WHO) criteria.[19]

Postoperative morbidity was graded according to the Clavien-Dindo classification.[20] Definition of postoperative hemorrhage and pancreatic fistula was based on the International Study Group of Pancreatic Surgery.[21,22] All patients were followed regularly in each participating institution. Disease recurrence was defined as identification of suspicious imaging findings on postoperative surveillance or biopsy-

proven recurrent pNET. Overall survival (OS) was calculated from the date of surgery to the date of death or date of last follow-up.

Statistical analysis

Numerical variables were expressed as medians with interquartile ranges (IQR) and compared with student *t* test or Mann-Whitney U test between the two groups. Nominal variables were expressed as number and percentages and compared with Chi-squared test or Fisher's exact test. Survival probabilities were estimated by Kaplan–Meier methodology and compared by log-rank analysis. Two-tailed *p*-values < 0.05 were considered statistically significant. Potential risk factors associated with OS and tumor recurrence were identified using univariate and multivariable Cox hazard regression models. Results were reported as hazard ratios (HR) and 95% confidence intervals (95% CI). Propensity score matching (PSM) was used to mitigate selection bias. Specifically, variables potentially affecting long-term outcomes were utilized in the propensity score based on identification in logistic regression analysis. Propensity score analysis with 1:1 matching was performed without replacement using a caliper with a width 0.05 of the standard deviation to generate matched pairs of the patients. In all analyses, two-tailed *p* value ＜0.05 was considered statistically significant. Statistical analysis was carried out using SPSS 22.0 (Chicago, IL, USA).

Results

A total of 1,020 patients undergoing curative-intent resection for pNET were included (**Figure 1**). Classic PD was performed in 129 patients, pylorus-preserving pancreaticoduodenectomy (PPPD) in 159 patients, central pancreatectomy (CP) in 32 patients, distal pancreatectomy (DP) in 576 patients, total pancreatectomy (TP) in 17 patients and tumor enucleation in 107 patients. Minimally invasive surgery (MIS) was mainly performed among patients undergoing DP; 214 patients who underwent MIDP, 25 patients who underwent laparoscopic/robotic converted to ODP, and 337 patients who underwent ODP were included in analytic cohort. Utilization of MIDP increased over time (2000-2004, 9.3%; 2005-2008, 14.5%; 2009-2012, 41.8%; 2013-2016, 54.8%, $p<0.01$ for trend)(**Figure 2**). In addition, the conversion rate of MIDP to open decreased (2000-2004, 20.0%; 2005-2008, 29.6%, 2009-2012, 7.8%, 2013-2016, 7.6%) (**Supplementary Table 1**).

Analytic Cohort

Among the 576 patients who underwent curative DP for pNET, median age was 58 (IQR 48-66) years with a slight female predominance (n=314, 54.5%). A majority of patients (n=490, 85.1%) presented with non-functional tumors and had no specific genetic syndrome (n=512, 88.9%); almost half of patients (n=276, 47.9%) were symptomatic. Most patients had a single (n=510, 88.5%), small (≤ 3 cm, n=375, 65.1%) mass and a well differentiated tumor (n=443, 76.9%). Most tumors (n=386, 67.0%) were located in the pancreatic tail. Following surgery, roughly one-half of patients (n=304, 52.8%) experienced at least one complication, while 113 (19.6%) patients experienced a

severe complication (Clavien-Dindo III-V); 22 (3.8%) patients required re-operation due to bleeding (n=9), intra-abdominal abscess (n=6), intestinal obstruction (n=3), and unknown reasons (n=4) (**Table 1**).

The clinicopathologic characteristics and surgical details among patients undergoing MIDP (n=214, 37.2%) and ODP (n=362, 62.8%) were assessed (**Table 1**). Compared with OPD, MIDP was more likely to be performed among patients with a single (MIDP 93.9% vs. OPD 85.4%, p=0.002) smaller tumor (≤ 3 cm, MIDP 73.4% vs. OPD 60.2%, p=0.001). In addition, concomitant splenectomy (MIDP 75.7% vs. OPD 87.0%, p=0.001) and additional pancreatic enucleation (MIDP 0.5% vs. OPD 4.1%, p=0.002) were less frequently performed among patients undergoing MIDP versus OPD. MIDP was associated with less intraoperative blood loss than OPD (median, 100 versus 300 ml, p<0.001), yet operative time (median, 210 minutes versus 210), as well as final WHO classification and tumor grade were similar among patients undergoing MIDP versus OPD (all p>0.05). The number of lymph node retrieved (median, 9 versus 8, p=0.709) were equivalent among MIDP and OPD. Interestingly, the median number of lymph nodes harvested increased over time among patients undergoing both MIDP (2000-2004, 3 nodes vs. 2013-2016, 10 nodes) and OPD (2000-2004, 3 nodes vs. 2013-2016, 13 nodes)(**Supplementary Table 1**, both p<0.05). In contrast, the incidence of R0 resection was higher among patients undergoing MIDP versus OPD (91.6% vs. 83.4%, p=0.005). MIDP was also associated with lower overall post-operative morbidity (47.7% vs. 55.8%, p=0.046), as well as a lower incidence of wound infection (2.3% vs. 6.1%, p=0.042), severe complications (13.1% vs. 23.3%, p=0.017), and a shorter in-hospital stay (median 5 days vs. 7 days, p=0.007) versus OPD (**Table 1**). Of note, while the

length-of-stay did not differ over time in the OPD group, the length-of-stay did decrease from a median of 9 days to 4 days in the MIDP group (**Supplementary Table 1**).

Long-term Outcomes

With a median follow up of 35.4 months (IQR 11.9-62.0 months), 77 (13.4%) patients developed recurrence (MIDP, 3.7% vs. ODP, 19.1%) and 53 (9.2%) patients died (MIDP, 5.1% vs. ODP, 11.6%). Overall 3-, 5- and 10-year cumulative recurrence was 2.7%, 8.9% and 8.9% among patients who had MIDP versus 18.4%, 25.9% and 42.7% among individuals who underwent ODP, respectively (HR 0.2, 95% CI 0.1-0.5, p<0.001)(**Figure 3a**). In contrast, OS was comparable among patients undergoing MIDP and ODP (3-, 5- and 10-year OS, MIDP 92.8%, 91.2% and 91.2% versus ODP 94.0%, 90.1% and 72.9%, p=0.300)(**Figure 3b**).

As the baseline characteristics among patients undergoing MIDP and ODP were different, propensity score matching (PSM) was utilized to generate 141 pairs of matched patients with similar functional status, tumor size, number, classification, as well as proportion of splenectomy, vascular resection, number of lymph node evaluated, number of metastatic nodes, margin status, and lymph-vascular invasion (**Supplementary Table 2**). In the propensity model, patients who underwent MIDP had less blood loss (median, MIDP 100 [50-150] vs. ODP 200 [105-500] ml, p<0.001) and a lower incidence of severe complications (Clavien-Dindo III-V) (MIDP 12.1% vs. ODP 24.8%, p=0.026), although overall morbidity was equivalent (**Table 2**). Perhaps not surprisingly, MIDP remained associated with a shorter in-hospital stay versus ODP (median, 4 [4-6] versus 7 [5-9] days, p=0.026) (**Table 2**). Of note, in the propensity model, patients who underwent

MIDP had a lower incidence of recurrence (5-year cumulative recurrence rate, MIDP 10.1% vs. ODP 31.1%, $p<0.001$)(**Figure 3c**), yet comparable OS (5-year OS, MIDP 92.1% vs. ODP 90.9% $p=0.550$) (**Figure 3d**). In assessing the entire cohort on multivariable analysis, history of a genetic syndrome (HR 2.5, 95% CI 1.1-5.8, $p=0.034$) and tumor size > 3 cm (HR 3.3, 95% CI 1.4-7.4, $p=0.005$) were associated with increased risk of tumor recurrence, whereas MIDP (versus ODP, HR 0.3, 95% CI 0.1-0.9, $p=0.033$) was associated with decreased tumor recurrence (**Table 3**). While MIDOP versus ODP was not associated with OS, tumor characteristics such as WHO G3 classification (ref. G1, HR 4.0, 95% CI 1.2-13.2, $p=0.001$) and poor tumor differentiation (ref. well differentiation, HR 2.3, 95% CI 1.2-6.7, $p=0.025$) were associated with worse OS (**Supplementary Table 3**).

Discussion

While minimally invasive surgery has been increasingly adopted for the treatment of pancreatic disease, the benefits of MIDP among patients with pNET remain not well described. The current study was important because, using a large multi-institutional cohort, we noted that utilization of MIDP versus ODP in treatment of pNET had dramatically increased over the last two decades in specialized centers throughout the United States. Perhaps more importantly, data from the current study demonstrated the short-term clinical advantages of MIDP versus ODP for pNET, including decreased intraoperative blood loss, as well as less risk of overall and severe post-operative morbidity and a shorter length of stay. Of note, ODP was more frequently performed among patients with advanced disease in terms of tumor size, number, vascular resection, and nodal involvement. As such, patients who underwent ODP had a higher incidence of

tumor recurrence than patients who underwent MIDP (5-year cumulative recurrence rate, ODP 31.1% vs. MIDP 10.1%, $p<0.001$). However, on both PSM and multivariate analysis, after controlling for some of these disparate risk factors, OS was equivalent among patients who underwent MIDP versus ODP.

The short-term benefits of MIDP versus ODP have been a topic of much interest. One systemic review and meta-analysis that included a total of 907 patients from eleven studies demonstrated comparable postoperative morbidity and mortality, as patients had the same incidence of pancreatic fistula, tumor recurrence and postoperative mortality.[3] MIDP was associated, however, with a shorter hospital stay and less blood loss. In contrast, a more recent meta-analysis by Drymousis and colleagues reported that patients who underwent laparoscopic surgery not only had lower blood loss and a shorter hospital stay, but also lower overall morbidity.[16] Both of these previous meta-analyses suffered, however, from the inclusion of mostly small single center reports that failed to included statistical methodology such as PSM to account for the heterogeneity among patients undergoing different surgical procedures. In contrast, the current study utilized PSM to help balance the MIDP and ODP cohorts. Of note, even after PSM, MIDP remained associated with decreased intraoperative blood loss, lower incidence of postoperative morbidity and a shorter hospital stay compared with ODP. In addition, patients who underwent MIDP had a lower incidence of severe complications. While a previous report reported comparable postoperative morbidity and mortality between MIDP and ODP, the study had suggested a superiority of MIDP over ODP for pancreatic ductal adenocarcinoma in terms of intraoperative blood loss and hospital stay.[23] A separate study by Xoufras and colleagues that examined patients who underwent DP for pNET

noted that laparoscopic DP was associated with a lower incidence of postoperative complications and a shorter hospital stay versus ODP.[24] Collectively the data strongly suggest that MIDP may be superior to ODP with regards to peri-operative outcomes including blood loss, complications and length-of-stay.

The current study showed a widespread and increased utilization of MIDP for pNET among major centers in the United States. In addition to the overall increase in the utilization of MIDP, the conversion rate decreased roughly from 20.0% before 2008 to 7.8% in 2009-2012 and 7.6% in 2013-2016. Braga et al. noted an overall conversion rate of 23.3 %, yet noted that the conversion rate dropped significantly after the first ten laparoscopic distal pancreatectomy cases.[25] In contrast, Shakir et al. noted that robotic distal pancreatectomy required 40 cases to optimize outcomes such as operative time and blood loss.[26] Interestingly, a temporal trend in the number of lymph nodes evaluated also increased over the time periods examined, while the incidence of severe complications and length-of-stay also both decreased. These data indicated that the increased use of MIDP over time has paralleled an increase in experience that has further augmented the beneficial peri-operative effects of the minimally invasive approach.

While the favorable peri-operative outcomes associated with MIDP have been generally accepted, the oncologic outcomes of MIDP versus ODP for pNET remain undetermined. Most previous reports reported only small groups of patients and data on surgical factors (e.g. margin status, lymphadenectomy) were not well defined. Data from our multi-institutional series demonstrated that some oncologic and surgical factors were comparable among patients who underwent MIDP versus ODP, yet other factors varied. For example, patients who underwent MIDP had a higher rate of R0 resection, which was

likely due to ODP patients presenting with more advanced disease (**Table 1**). The data did suggest, however, that MIDP was at least as effective as ODP in obtaining an adequate margin and lymph node evaluation. Patients who underwent ODP had a higher risk of recurrence that was almost undoubtedly related to differences in underlying tumor factors. To minimize the patient selection bias, we utilized PSM to create more balanced cohorts for comparison. On PSM, after balancing many tumor and surgical factors, patients who underwent MIDP still had a lower incidence of tumor recurrence, yet OS was equivalent to patients who underwent ODP. In a separate study by Xourafas et al., patients undergoing MIDP (n=78) for pNET similarly had comparable recurrence and OS versus individuals who underwent ODP.[24] Interestingly, the incidence of recurrence after MIDP was similar in the current study compared with the data from Xourafas et al. (3.7% vs. 4%), yet recurrence among the ODP group was considerably higher in the current study (19.1% vs. 4%).[24] The difference in recurrence was undoubtedly multifactorial and was likely related to differences in patient selection. For example, the incidence of R1 resection among patients undergoing ODP was higher in the current study than the study by Xourafas et al. (16.6% vs. 7%).[24] Of note, similar to the current study, DiNorcia et al. reported a higher tumor recurrence rate (15.3%) after open surgery versus minimally invasive procedures (4.4%) for pNET.[27] Theses authors postulated that the higher recurrence rate in the open surgery group was explained by more advanced disease on presentation.[27] Data from the current study, as well as several previous reports, strongly suggest at least non-inferior oncologic outcomes for MIDP versus ODP for the resection of pNET.

The current study had several limitations. Although the multi-institutional collaboration increased the sample size and generalizability of the results, possible inconsistency in patient selection, choice of MIDP or ODP, surgical skills and procedures, pathologic assessment and reporting, as well as postoperative surveillance likely existed. While known tumor and surgery related factors were matched between the MIDP and ODP groups using PSM, patients undergoing ODP still had pNET with more advanced tumor features versus MIDP in the matched cohort. Patients with smaller and low-grade tumor were more likely to undergo minimally invasive surgery. As such, residual confounding-by-indication persisted in comparing the MIDP versus ODP groups. Moreover, the outcome of patients undergoing minimally invasive surgery is largely influenced by the technical skills. However, the number of surgeons in each institution and their learning curves were not available in the current database. The current study also focused on DP; future studies will, therefore, need to assess the short- and long-term outcomes of minimally invasive versus open procedures for more complex surgery such as pancreaticoduodenectomy for pNET.

In conclusion, utilization of MIDP increased to more than one-half of all surgical procedures for pNET over the last two decades. Current conversion rates were less than 10% and MIDP was associated with less blood loss, a lower incidence of postoperative morbidity, and a shorter hospital stay compared with ODP. Data from the current study demonstrated comparable oncologic surgical metrics, as well as similar long-term OS among patients undergoing MIDP over ODP in treatment of pNET. As such, a minimally invasive approach to pNET tumors should be considered as the surgical approach of choice when technically feasible.

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Figures

Figure 1: Study scenario and patient selection. PNET, pancreatic neuroendocrine tumor; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; CP, central pancreatectomy; DP, distal pancreatectomy; TP, total pancreatectomy; MIS, minimally invasive surgery.

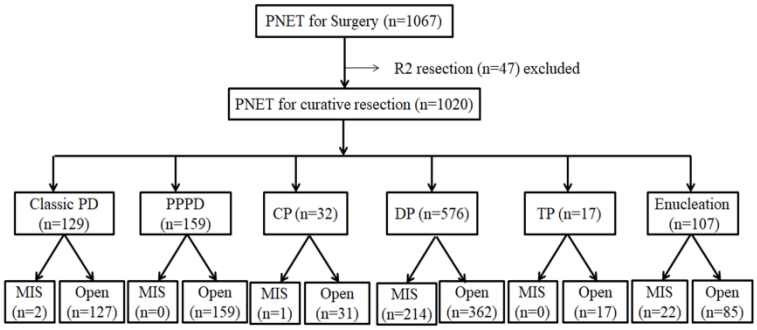

Figure 2: Utilization of minimally invasive distal pancreatectomy (MIDP) and open distal pancreatectomy (ODP) for pancreatic neuroendocrine tumor (pNET) at different time periods.

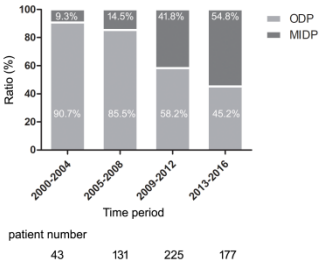

Figure 3: Cumulative tumor recurrence rate (a) and overall survival (b) among patients undergoing minimally invasive distal pancreatectomy (MIDP) and open distal pancreatectomy (ODP) for pancreatic neuroendocrine tumor (pNET) in unadjusted cohort. Cumulative tumor recurrence rate (c) and overall survival (d) among patients undergoing MIDP and ODP for pNET in adjusted cohort.

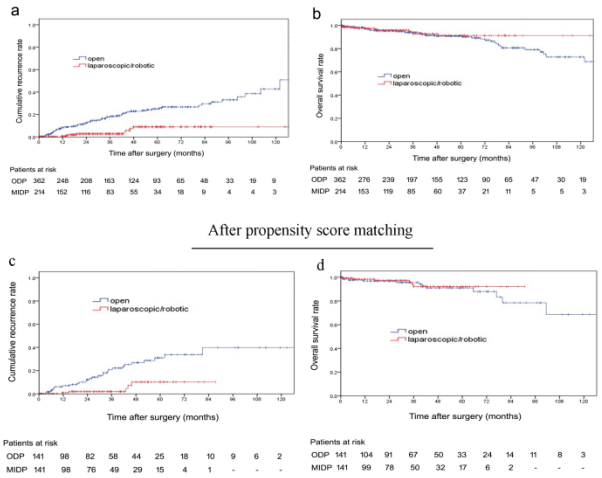

Table 1. Clinicopathologic characteristics and operation details of patients undergoing minimally invasive distal pancreatectomy (MIDP) versus open distal pancreatectomy (ODP) for pancreatic neuroendocrine tumors (pNETs).

	Overall (n=576)	MIDP (n=214)	ODP (n=362)	P value
Age (years)	58 (48-66)	59 (50-66)	56 (47-65)	0.414
Gender				0.489
Male	262 (45.5%)	93 (43.5%)	169 (46.7%)	
Female	314 (54.5%)	121 (56.5%)	193 (53.3%)	
BMI (kg/m^2)	28.4 (25.3-34.0)	29.2 (25.9-33.8)	28.2 (24.5-34.3)	0.359
Functional status				0.245
Non-functional	490 (85.1%)	179 (83.6%)	311 (85.9%)	
Functional	73 (12.7%)	32 (15.0%)	41 (11.3%)	
NA	13 (2.3%)	3 (1.4%)	10 (2.8%)	
Genetic syndrome				0.064
None	512 (88.9%)	199 (93.0%)	313 (86.5%)	
MEN 1	50 (8.7%)	12 (5.6%)	38 (10.5%)	
VHL	2 (0.3%)	0	2 (0.6%)	

NA	12 (2.1%)	3 (1.4%)	9 (2.5%)	
Symptomatic	276 (47.9%)	99 (46.3%)	177 (48.9%)	0.486
Primary location				<0.001
Neck/body	162 (28.1%)	46 (21.5%)	116 (32.0%)	
Tail	386 (67.0%)	165 (77.1%)	221 (61.0%)	
Multiple location	28 (4.9%)	3 (1.4%)	25 (6.9%)	
Largest tumor size (cm)				0.001
≤ 3	375 (65.1%)	157 (73.4%)	218 (60.2%)	
> 3	180 (31.3%)	49 (22.9%)	131 (36.2%)	
Tumor number				0.002
Single	510 (88.5%)	201 (93.9%)	309 (85.4%)	
multiple	66 (11.5%)	13 (6.1%)	53 (14.6%)	
Splenectomy	477 (82.8%)	162 (75.7%)	315 (87.0%)	0.001
Additional enucleation	16 (2.8%)	1 (0.5%)	15 (4.1%)	0.007
Major vascular resection	11 (1.9%)	0	11 (3.0%)	0.009
Pancreatic transection				<0.001
Hand-sewn	30 (5.2%)	3 (1.4%)	27 (7.5%)	

Stapled with no suture	220 (38.2%)	113 (52.8%)	107 (29.6%)	
Stapled with reinforcement	160 (27.8%)	49 (22.9%)	111 (30.6%)	
Other procedures	23 (4.0%)	7 (3.3%)	16 (4.4%)	
Missing	143 (24.8%)	42 (19.6%)	101 (27.9%)	
Intraoperative abdominal drainage	518 (89.9%)	189 (88.3%)	329 (90.9%)	0.132
Operation time (min)	210 (179-263)	210 (180-258)	210 (177-266)	0.652
Estimated blood loss (ml)	200 (100-400)	100 (50-150)	300 (150-500)	<0.001
Lymphadenectomy	509 (88.4%)	187 (87.4%)	322 (89.0%)	0.331
No. of lymph node retrieved	9 (4-14)	9 (4-14)	8 (4-14)	0.709
Lymph nodes status				0.001
Negative	411 (71.4%)	166 (77.6%)	245 (67.7%)	
Positive	99 (17.2%)	22 (10.3%)	77 (21.3%)	
Tumor differentiation				0.824
Well differentiated	443 (76.9%)	173 (80.8%)	270 (74.6%)	
Moderately differentiated	53 (9.2%)	23 (10.7%)	30 (8.3%)	
Poorly differentiated	8 (1.4%)	3 (1.4%)	5 (1.4%)	

NA	72 (12.5%)	15 (7.0%)	57 (15.7%)	
Margin status				0.005
R0	498 (86.5%)	196 (91.6%)	302 (83.4%)	
R1	78 (13.5%)	18 (8.4%)	60 (16.6%)	
Ki-67				0.040
<3%	242 (42.0%)	118 (55.1%)	124 (34.3%)	
3-20%	141 (24.5%)	50 (23.4%)	91 (25.1%)	
>20%	12 (2.1%)	5 (2.3%)	7 (1.9%)	
Mitotic rate				0.485
<2	291 (50.5%)	134 (62.6%)	157 (43.4%)	
2-20	57 (9.9%)	23 (10.7%)	34 (9.4%)	
>20	1 (0.2%)	0	1 (0.3%)	
WHO classification				0.712
G1	304 (52.8%)	124 (57.9%)	180 (49.7%)	
G2	138 (24.0%)	53 (24.8%)	85 (23.5%)	
G3	13 (2.3%)	4 (1.9%)	9 (2.5%)	
Unknown	121 (21.0%)	33 (15.4%)	88 (24.3%)	

Lymph-vascular invasion				<0.001
Absent	357 (62.0%)	162 (75.7%)	195 (53.9%)	
Present	122 (21.2%)	31 (14.5%)	91 (25.1%)	
Perineural invasion				0.065
Absent	360 (62.5%)	155 (72.4%)	205 (56.6%)	
Present	71 (12.3%)	22 (10.3%)	49 (13.5%)	
Postoperative morbidity	304 (52.8%)	102 (47.7%)	202 (55.8%)	0.046
Clavein-Dindo classification				0.023
I	83 (14.4%)	39 (18.2%)	44 (12.2%)	
II	108 (18.8%)	35 (16.4%)	73 (20.2%)	
IIIa	67 (11.6%)	13 (6.1%)	54 (14.9%)	
IIIb	15 (2.6%)	4 (1.9%)	11 (3.0%)	
IVa	19 (3.3%)	7 (3.3%)	12 (3.3%)	
IVb	6 (1.0%)	1 (0.5%)	5 (1.4%)	
V	6 (1.0%)	3 (1.4%)	3 (0.8%)	
Severe complication (III-V)	113 (19.6%)	28 (13.1%)	85 (23.3%)	0.017
Postoperative hemorrhage	13 (2.3%)	5 (2.3%)	8 (2.2%)	1.000

Pancreatic fistula				0.915
A	88 (15.3%)	31 (14.5%)	57 (15.7%)	
B	57 (9.9%)	20 (9.3%)	37 (10.2%)	
C	4 (0.7%)	1 (0.5%)	3 (0.8%)	
Wound infection	27 (4.7%)	5 (2.3%)	22 (6.1%)	0.042
Wound disruption	11 (1.9%)	2 (0.9%)	9 (2.5%)	0.225
Intraabdominal infection	64 (11.1%)	16 (7.5%)	48 (13.3%)	0.038
Postoperative drainage	74 (12.8%)	16 (7.5%)	58 (16.0%)	0.003
Length of stay (d)	6 (5-8)	5 (4-6)	7 (5-9)	0.007
Reoperation	22 (3.8%)	7 (3.3%)	15 (4.1%)	0.659

Table 2. Postoperative morbidity of patients undergoing minimally invasive distal pancreatectomy (MIDP) versus open distal pancreatectomy (ODP) for pancreatic neuroendocrine tumors (pNETs) in propensity model.

	MIS (n=141)	Open (n=141)	P value
Postoperative morbidity	68 (48.2%)	82 (58.2%)	0.094
Clavein-Dindo classification			0.072
I	30 (21.3%)	17 (12.1%)	
II	21 (14.9%)	30 (21.3%)	
IIIa	9 (6.4%)	20 (14.2%)	
IIIb	3 (2.1%)	6 (4.3%)	
IVa	4 (2.8%)	5 (3.5%)	
IVb	0	2 (1.4%)	
V	1 (0.7%)	2 (1.4%)	
Severe complication (III-V)	17 (12.1%)	35 (24.8%)	0.026
Postoperative hemorrhage	4 (2.8%)	3 (2.1%)	1.000
Pancreatic fistula			0.651
A	24 (17.0%)	28 (19.9%)	
B	15 (10.6%)	14 (9.9%)	

C	0	0	
Wound infection	1 (0.7%)	5 (3.5%)	0.214
Wound disruption	1 (0.7%)	5 (3.5%)	0.214
Intraabdominal infection	8 (5.7%)	14 (9.9%)	0.266
Postoperative drainage	11 (7.8%)	20 (14.2%)	0.090
Length of stay (d)	4 (4-6)	7 (5-9)	0.026
Reoperation	3 (2.1%)	7 (5.0%)	0.217

Table 3. Factors associated with tumor recurrence after curative resection of pancreatic neuroendocrine tumors (pNETs).

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Functional status		0.737		
Non-functional	Ref.			
Functional	0.7 (0.1-5.1)			
Genetic syndrome		0.017		**0.034**
Not associated	Ref.		Ref	

Associated	1.9 (1.1-3.3)		2.5 (1.1-5.8)	
Symptomatic		0.016		0.701
No	Ref.		Ref.	
Yes	1.8 (1.1-2.8)		1.1 (0.6-2.3)	
Surgery technique		<0.001		**0.033**
Open	Ref.		Ref.	
Laparoscopic/robotic	0.2 (0.1-0.5)		0.3 (0.1-0.9)	
Major vascular resection	5.0 (2.0-12.5)	0.001	2.0 (0.5-7.3)	0.321
Splenectomy	2.2 (1.1-4.8)	0.046	1.5 (0.4-5.6)	0.527
Tumor size (cm)		<0.001		**0.005**
≤ 3	Ref.		Ref.	
> 3	5.6 (3.4-9.3)		3.3 (1.4-7.4)	
Multiple lesions	1.0 (0.5-1.9)	0.966		
Surgical margin		0.009		0.389
R0	Ref.		Ref.	
R1	2.0 (1.2-3.4)		1.5 (0.6-3.5)	
Tumor differentiation				

Well differentiated	Ref.		Ref.	
Moderately differentiated	2.0 (1.0-3.8)	0.043	0.8 (0.3-2.3)	0.655
Poorly differentiated	8.1 (2.9-22.6)	<0.001	3.8 (0.4-33.4)	0.228
Nodal status		<0.001		0.517
N0	Ref.		Ref.	
N1	2.8 (1.7-4.4)		0.8 (0.3-1.7)	
WHO classification				
G1	Ref.		Ref.	
G2	3.2 (1.8-5.6)	<0.001	2.1 (0.9-4.8)	0.092
G3	12.8 (5.3-30.5)	<0.001	4.1 (0.8-20.7)	0.088
Lymph-vascular invasion	3.9 (2.3-6.7)	<0.001	1.5 (0.7-3.5)	0.308
Perineural invasion	1.6 (0.9-3.1)	0.139		