Published in final edited form as:

Ann Surg. 2022 September 01; 276(3): 522–531. doi:10.1097/SLA.0000000000005559.

Long term outcomes of parenchyma-sparing and oncologic resections in patients with non- functional pancreatic neuroendocrine tumors <3cm in a large multi-center cohort

Louisa Bolm, MD[(1),*], **Martina Nebbia, MD**[(1),*], **Alice C. Wei, MD**[(2)], **Amer H. Zureikat, MD**[(3)], **Carlos Fernández-del Castillo, MD**[(1)], **Jian Zheng, MD**[(3)], **Alessandra Pulvirenti, MD**[(2)], **Ammar A. Javed, MD**[(4)], **Yurie Sekigami, MD**[(1)], **Natalie Petruch**[(1)], **Motaz Qadan, MD PhD**[(1)], **Keith D. Lillemoe, MD**[(1)], **Jin He, MD**[(4),±], **Cristina R. Ferrone, MD**[(1),±], **the PAncreatic Neuroendocrine Disease Alliance (PANDA)**

(1) Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

(2) Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

(3) Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA

(4) Department of Surgery, Johns Hopkins Hospital, Baltimore, MD

Abstract

Introduction: The role of parenchyma-sparing resections (PSR) and lymph node dissection in small (<3cm) non-functional pancreatic neuroendocrine tumors (PNET) is unlikely to be studied in a prospective randomized clinical trial. By combining data from 4 high volume pancreatic centers we compared postoperative and long-term outcomes of patients who underwent PSR with patients who underwent oncologic resections.

Patients and Methods: Retrospective review of prospectively collected clinicopathologic data of patients who underwent pancreatectomy between 2000 and 2021 was collected from four high volume institutions. Parenchyma- and lymph node-sparing resections (enucleation and central pancreatectomy) were compared to those who underwent oncologic resections with lymphadenectomy (pancreaticoduodenectomy, distal pancreatectomy). Statistical testing was

Corresponding Author: Cristina R. Ferrone, MD, Department of Gastrointestinal Surgery, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St, Boston, MA-02114, United States, CFERRONE@mgh.harvard.edu.

Authors' contributions:

Conception and design of the study: Louisa Bolm, Martina Nebbia, Cristina R. Ferrone; Acquisition of data: Martina Nebbia, Alice C. Wei, Amer H. Zureikat, Jian Zheng, Alessandra Pulvirenti, Ammar A. Javed, Yurie Sekigami, Natalie Petruch, Jin He, Cristina R. Ferrone; Analysis and interpretation of the data: Louisa Bolm, Martina Nebbia, Alice C. Wei, Amer H. Zureikat, Jian Zheng, Alessandra Pulvirenti, Ammar A. Javed, Yurie Sekigami, Natalie Petruch, Jin He, Cristina R. Ferrone, Keith Lillemoe, Motaz Qadan, Carlos Fernández-del Castillo; Drafting the manuscript: Louisa Bolm, Martina Nebbia, Cristina R. Ferrone; Revising the manuscript for intellectual content: Alice C. Wei, Amer H. Zureikat, Jian Zheng, Alessandra Pulvirenti, Ammar A. Javed, Yurie Sekigami, Natalie Petruch, Jin He, Cristina R. Ferrone, Keith Lillemoe, Motaz Qadan, Carlos Fernández-del Castillo; Approval of the final version to be published: Louisa Bolm, Martina Nebbia, Cristina R. Ferrone, Alice C. Wei, Amer H. Zureikat, Jian Zheng, Alessandra Pulvirenti, Ammar A. Javed, Yurie Sekigami, Natalie Petruch, Jin He, Keith Lillemoe, Motaz Qadan, Carlos Fernández-del Castillo

[*]Louisa Bolm and Martina Nebbia contributed equally and share first authorship.

[±]Cristina Ferrone and Jin He contributed equally and share senior authorship.

Conflicts of Interest and Source of Funding:

The authors declare no conflict of interest.

performed using Chi- squared test and t test, survival estimates with Kaplan Meier method and multivariate analysis using Cox proportional hazard model.

Results: Of 810 patients with small sporadic non-functional PNETs, 121 (14.9%) had enucleations, 100 (12.3%) had central pancreatectomies and 589 (72.7%) patients underwent oncologic resections. The median age was 59 years and 48.2% were female with a median tumor size of 2.5 cm. After case- control matching for tumor size, 221 patients were selected in each group. Patients with PSR were more likely to undergo minimally invasive operations (32.6% vs. 13.6%, p<0.001), had less intraoperative blood loss (358 ml vs. 511 ml, p<0.001) and had shorter operative times (180 min vs. 330 min, p<0.001) than patients undergoing oncologic resections. While the mean number of lymph nodes harvested was lower for PSR (n=1.4 vs. n=9.9, p<0.001), the mean number of positive lymph nodes was equivalent to oncologic resections (n=1.1 vs. n=0.9, p=0.808). Although the rate of all postoperative complications was similar for PSR and oncologic resections (38.5% vs. 48.2%, p=0.090), it was higher for central pancreatectomies (38.5% vs. 56.6%, p=0.003). Long-term median disease-free survival (DFS) (190.5 m vs. 195.2 m, p=0.506) and overall survival (OS) (197.9 m vs. 192.6 m, p=0.372) were comparable.

Of the 810 patients 136 (16.7%) had no lymph nodes resected. These patients experienced less blood loss, shorter operations (p<0.001), and lower postoperative complication rates as compared to patients who had lymphadenectomies (39.7% vs. 56.9%, p=0.008). Median DFS (197.1m vs. 191.9m, p=0.837) and OS (200m vs. 195.1m, p=0.827) were similar for patients with no lymph nodes resected and patients with negative lymph nodes (N0) after lymphadenectomy.

Conclusion: In small <3cm non-functional PNETs, parenchyma- and lymph node-sparing resections are associated with lower blood loss, shorter operative times, and lower complication rates when compared to oncologic resections, and have similar long-term oncologic outcomes.

Mini-Abstract

The aim of the study is to compare postoperative and long-term outcomes of patients who underwent parenchyma-sparing resections with patients who underwent oncologic resections for pancreatic neuroendocrine tumors. In small non-functional PNETs, parenchyma-sparing resections are associated with lower blood loss, shorter operative times, and lower complication rates when compared to oncologic resections, and have similar long-term oncologic outcomes.

Introduction

Pancreatic neuroendocrine tumors (PNET) are a rare entity and represent only 1–2% of all pancreatic neoplasms[1,2]. The majority of PNETs are non-functional and identified incidentally[3]. A small percentage are functional or symptomatic and require surgical resection[4]. However, the management of small sporadic non-functional PNETs continues to be controversial. Small retrospective studies with limited follow-up suggest that observation is equivalent to resection in small PNETs <2cm[5–7]. The European Neuroendocrine Tumor Society (ENETS) Guidelines and the North American Neuroendocrine Tumor Society Consensus Guidelines, however, propose parenchyma-sparing resections (PSR) like enucleation or central pancreatectomy for sporadic non-functional PNETs smaller than 2cm[8,9]. Yet, the long-term outcomes of PSR and oncologic resections have never been studied in a clinical trial.

The advantage of PSR includes preservation of endocrine and exocrine pancreatic function[10]. However, these procedures bear a higher risk of positive resection margins and do not include oncologic lymph node dissections[11]. Currently, insufficient data exist in the literature to determine whether parenchyma-sparing resections or oncologic resections portend an improved disease-free and overall survival.

The role of PSR and lymph node dissection in small (<3cm) non-functional PNETs is unlikely to be studied in a prospective randomized clinical trial. By combining data from 4 high volume centers we aimed to determine the long-term oncologic outcomes of patients who underwent PSR to patients who underwent oncologic resections for PNETs <3cm.

Methods

Patients and study parameters

Approval for the study was obtained from the IRB of all participating institutions. Patients who underwent PSR (enucleation, central pancreatectomy) or oncologic resections (pancreatoduodenectomy (PD), distal pancreatectomy, or total pancreatectomy) for PNETs were identified from prospectively maintained databases of the participating centers. Patients with functional tumors, hereditary syndromes, multifocal disease, distant metastases, and tumors larger than 3cm were excluded from the study. The study period spanned from 2000 to 2021. The following patient baseline parameters were obtained: age, gender, ASA score, body mass index (BMI). ASA score was dichotomized as I-II and III-IV. Operative procedures were PSR such as enucleation and central pancreatectomy as well as oncologic resections including pancreatoduodenectomy, distal and total pancreatectomy. At all centers, patients were considered for a PSR when it appeared technically feasible and there was no evidence of potential lymph node metastasis. Operative parameters analyzed in the study were minimal-invasive procedures, intraoperative blood loss in ml and operation time in min. Lymph node resection was classified as lymph node-sparing resection, lymph node resection with negative lymph nodes and lymph node resection with positive lymph nodes. Lymph node-sparing resections were performed if the multidisciplinary team determined lymph node involvement as unlikely and decided to perform neither standard lymphadenectomy nor lymph node sampling.

Histopathological parameters evaluated in the analysis were tumor size, T stage, N stage, Ki-67 index, grading according to the 2010 WHO classification[12], R status, number of lymph nodes harvested, number of positive lymph nodes, lymphovascular invasion and perineural invasion (PNI). T stage was dichotomized as T1–2 versus T3–4 and grading was dichotomized as G1 versus G2–3. Ki-67 index was dichotomized to Ki-67 index <3 and >3. R status was according to UICC/AJCC criteria as R0 if no tumor cells were detected at the resection margin versus R1 if tumor cells were present less than 1mm from the resection margin[13]. TNM staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC)[14]. Postoperative parameters were postoperative complications, postoperative morbidity according to the Clavien-Dindo Classification, clinically relevant postoperative pancreatic fistula (POPF)[15], postoperative pancreatic hemorrhage (PPH)[16], delayed gastric emptying (DGE)[17], reoperation postoperative

mortality within 30 days. Overall survival time was defined from surgery until death of any cause, and disease-free survival was from surgery until recurrence.

Statistics

Descriptive missing data analysis with percentage missing data per variable and per case as well as missing data patterns was performed. Assuming missing as random process, multiple imputations for missing data using the chained equations method was implemented with the R package mice for data imputation[18] in case of less than 10% missing data per variable and per case[18]. Continuous and categorical variables were expressed as mean/standard error and absolute/relative frequencies. A 1:1 propensity score-based matching was performed for baseline parameters of patients with PSR and oncological resection (variables: age, gender, ASA score, BMI). A1:1 matching of both groups for tumor size was based on the ‘nearest-neighbor method’. Statistical testing was performed by Chi- squared test for categorial variables, and Student t test for continuous variables. Median overall and recurrence-free survival estimates were determined with Kaplan Meier method, and log-rank-test and survival analyses were performed with Cox proportional hazard model. The significance level was set to $p < 0.05$ (two-sided). All confidence intervals (CI) reported were 95% confidence intervals. For statistical analysis, IBM SPSS Statistics for Windows, version 25, was used.

Results

Patient baseline parameters

A total of 1742 patients underwent pancreatic resections for PNETs from 2000 to 2021 and were identified from prospectively maintained databases at the four participating centers. After excluding patients with distant metastasis, multifocal PNETs, hereditary syndromes, functional tumors and a tumor size of more than 3 cm, 810 patients remained and were included in the study. PSR were performed in 221 (27.3%) patients, while 589 (72.7%) underwent oncologic resections. Median age was 59 years and 392 (48.4%) patients were female. Baseline characteristics and histopathological parameters of these patients are displayed in table 1.

For these 810 patients the median follow-up time was 208 months, disease-free survival (DFS) and overall survival (OS) were 180 months and 195 months (Fig. 1). On multivariate analysis Ki67 index (HR 6.482, 95%CI 1.947–8.978, p=0.002) and vascular invasion (HR 2.875, 95%CI 1.191–6.943, p=0.019) are prognostic for DFS, while ASA score (HR 4.045, 95%CI 1.753–9.332, p=0.001) is prognostic for OS. A total of 128 patients (15.8%) had positive lymph nodes (N+). As compared to patients with N0 (n=546), N+ patients experienced a shorter DFS (117.1 m vs. 191.9 m, p<0.001) and OS (169.1 m vs. 195.1 m, p<0.001).

Propensity score-based matching

For propensity score matching 221 patients with PSR were compared to 221 patients undergoing oncologic resections. Baseline parameters including age, gender, ASA score, and BMI were well- balanced in the two groups (Table 2). For patients undergoing PSR 121

patients (14.9%) had an enucleation and 100 patients (12.3%) had a central pancreatectomy, while for those undergoing oncologic resections 75 had a pancreatoduodenectomy (33.9%), 144 a distal pancreatectomy (65.1%) and 2 a total pancreatectomy (1.0%). PSR were more frequently performed minimally-invasively than oncologic resections (32.6% vs. 13.6%, p<0.001). Patients undergoing PSR experienced reduced blood loss (mean 209.1 ml vs. 511.2 ml, p<0.001) and shorter operative times (mean 180 min vs. 330 min, p<0.001) than patients undergoing oncologic resections.

Histopathology

Despite propensity score matching, patients undergoing PSR had a lower rate of T3–4 tumors (8.6% vs. 20.4%, p<0.001) and had a higher R+ resection rate (26.2% vs. 8.1%, p<0.001) than patients who had oncologic resections (Table 2). PSR resulted in a lower number of lymph nodes harvested (median 0 vs. 9, p<0.001), however, the median number of positive lymph nodes (0 vs. 0, p=0.808) and the rate of N1 disease (6.7% vs. 7.7%, p=0.999) did not differ between patients undergoing PSR or oncologic resections. High risk features such as perineural invasion (8.9% vs. 21.8%, p<0.001), WHO grade 2–3 tumors (13.1% vs. 23.6%, p<0.001) and Ki-67 >3 (13.1% vs. 18.6%, p<0.001) were also less commonly identified in PNETs undergoing PSR as compared to oncologic resections in the matched cohorts.

Long-term Outcomes

OS and DFS did not differ between patients undergoing a PSR or an oncologic resection in the matched cohorts (Fig. 1). Interestingly when examining the whole cohort of 810 patients, as well as the two subgroups, DFS did not differ between patients with negative and those with microscopically positive resection margins (R0 193 m vs. R1 152 m, p=0.90). A total of 95 (11.7%) patients had positive resection margins, of which 58 patients had PSR. Unlike DFS, OS for the total cohort of patients was decreased in patients with positive margins as compared to those with negative resection margins (204 m vs. 144 m, p<0.001). Importantly, margin status did not affect OS in patients with negative lymph nodes (n=410, R0 208.6 m vs. R1 201.8 m, p=0.65), but did for patients with positive resection margins (n= 32, R0 172.8 m vs. R1 110.2 m, p=0.05) (Table 3).

In the matched cohort, 152 (34.4%) patients had a tumor size of less than 2 cm and 290 (65.6%) patients had tumors larger than 2 cm. DFS for PSR and oncologic resections were equivalent in patients with PNETs < 2cm (PSR 200.4 m vs. oncologic resection 200.6 m, p=0.73) and those > 2cm (PSR 174.6 m vs. oncologic resection 176.3 m, p=0.95). There was also no difference in OS for either procedure in patients with PNETs smaller than 2cm (PSR 210.7 m vs. oncologic resection 215.4 m, p=0.430) or larger than 2cm (PSR 187.2 m vs. oncologic resection 175.1 m, p=0.73).

Postoperative morbidity

Postoperative complication rates for enucleations (n=121) and central pancreatectomies (n=100) were compared to oncologic resections (Table 4). Enucleations demonstrated a trend for higher postoperative complication rates (48.4% vs. 38.5%, p=0.09) and higher rates of severe postoperative complications >IIIA according to the Clavien-Dindo Classification

(19.0% vs. 11.8%, p=0.08), but not an increase in 30 day post operative mortality. The most common severe complications were POPF grade B-C in 21.3% of patients with enucleations. There was a trend for higher POPF grade B-C rates in patients with enucleations as compared to oncologic resections (21.3% vs. 8.1%, p=0.09). There was no difference for DGE or PPH.

Central pancreatectomies were associated with a higher rate of postoperative morbidity (56.6% vs. 38.5%, p=0.003) and a higher rate of severe postoperative complications >IIIA according to the Clavien Dindo Classification (19.2% vs. 11.8%, p=0.04) as compared to oncologic resections. Central pancreatectomy patients experienced higher rates of POPF grade B/C (20.2% vs. 8.1%, p=0.03) and post-pancreatectomy hemorrhage (5.1% vs. 0.0%, p=0.02) as well as higher reoperation rates (4.0% vs. 0.5%, p=0.03) but no higher 30 day post operative mortality than patients undergoing oncologic resections.

Lymph-node-sparing procedures versus lymph node dissection

In the total cohort of 810 patients, 136 (16.8%) patients had no lymph nodes harvested and 674 patients had at least one lymph node removed. Positive lymph nodes were identified in 128 (15.8%) patients. There were no statistically significant differences in age, gender, BMI and ASA score between patients who had no lymph nodes harvested and those patients undergoing lymph node dissection with negative lymph nodes (LND-N0) and patients undergoing lymph node dissection with positive lymph nodes (LND-N+). Tumors in the group with no LNs harvested and LND-N0 were more often located in the body and tail of the pancreas (83.8% and 64.8%), while the majority of patients in the LND-N+ group had pancreatic head tumors (67.2%, p<0.001). Patients who had no LNs harvested were more likely to undergo PSR as compared to LND-N0 and LND-N+ patients (66.2% vs. 7.3% vs. 4.7%, p<0.001) and more commonly underwent minimally invasive procedures (38.5%). When no LNs were harvested it was associated with reduced blood loss (mean 225.1 ml vs. 378.9 ml vs. 471.4 ml, p<0.001), shorter operative times (mean 177.7 min vs. 262.3 min vs. 297.5 min, p<0.001), and lower rates of postoperative morbidity (39.7% vs. 53.1% vs. 47.0%, p=0.008) as compared to LND- N0 and LND-N+ patients. Patients who had no LNs resected experienced lower rates of DGE (2.4% vs. 12.9% vs. 14.4%, p=0.02), but there was no difference in POPF grade B/C, reoperation rates, or postoperative morbidity when compared to patients undergoing lymph node dissections (Table 5).

Patients who had no LNs harvested (n= 136) experienced DFS and OS rates equivalent to N0 patients (n= 546) (197.1 m vs. N0 191.9 m, p=0.74 and 200.0 m vs. N0 195.1 m, p=0.87).

Discussion

The surgical approach to small (<3cm) non-functional pancreatic neuroendocrine tumors (PNET) is unlikely to be studied with a prospective randomized clinical trial. By assembling a large cohort of patients from four high-volume centers we aimed to provide guidance on the oncologic safety and clinical decision making for these patients. We demonstrated that parenchyma-sparing resections (PSR) and lymph node-sparing procedures are oncologically safe for both PNETs < 2cm and those 2–3cm. Despite higher margin positive resection rates

in PSR, long-term oncologic outcomes of PSR and oncologic resection were equivalent. In this cohort of 810 patients, oncologic operations such as pancreaticoduodenectomy and distal pancreatectomy increased postoperative morbidity and did not improve patient prognosis.

Improved imaging modalities have led to an increased rate of incidentally discovered small sporadic non-functional PNETs[19]. While the NANET and ENET guidelines, based on retrospective studies, recommend observation for small non-functioning PNETs <2cm with no evidence of invasion, the surgical management of PNETs <3cm remains controversial[20]. For lesions <2cm, the ongoing prospective observational trial evaluating oncologic safety of observation in PNETs < 2cm will allow for improved evidence based guidance (ASPEN, NCT03084770)[21].

For those patients who are considered for surgical removal of their PNETs PSR compared to oncologic resections have been actively debated. Large cohort studies and meta-analyses have shown that PSR helps to preserve endocrine and exocrine pancreatic function[19,22,23]. Ideal candidates for PSR are PNETs with low-risk histologic and anatomical features. However, these criteria are not met in all cases, and a negative resection margin cannot always be obtained[24]. Additionally, a complete oncologic lymph node dissection is difficult to perform when sparing pancreatic parenchyma[11]. For small sporadic PNETs large cohort studies evaluating the effect of a PSR compared to an oncologic operation on long-term outcomes have not been performed. The role of lymph node dissection has also not been extensively evaluated. Due to these many unanswered questions, the rate of PSR remains low (12–17.7%)[25].

To understand if an oncologic operation is required to optimize long-term outcomes for patients with PNETS <3cm we compared patients who underwent PSR such as enucleation or central pancreatectomy to those who had an oncologic resection, such as a Whipple or distal pancreatectomy and splenectomy. Enucleations were associated with the highest rate of positive resection margins, similar to other studies documenting an R1 resection in 16–32%[19,25–27]. Despite a higher rate of microscopically positive margins (26% vs 8%) and a lower number of lymph nodes harvested with PSR, DFS (190m vs. 195 m) and OS (197 m vs. 192m) were equivalent between the two cohorts.

Interestingly, R status was a determinant of OS but not DFS in the entire cohort of 810 patients (204 m vs. 144 m). Looking at subgroups of N0 and N1 patients, R status remained a prognostic factor for OS only in N1 patients (R0 172.8 m vs. R1 110.2 m). In summary, R status appears not to impact long- term outcomes in patients undergoing PSR or oncologic resections if lymph nodes are not involved, as opposed to patients who have nodal involvement.

Our results compare to smaller cohort studies investigating long-term outcomes and the oncologic safety of PSR. Cherif et al. compared 67 patients with enucleations and central pancreatectomies to 66 patients with standard oncologic resections[28]. Patients included in this study had a median tumor size of 15 mm (range 3–40mm). The overall and recurrence-free 5-year survival after PSR for non- functional tumors was as high as 96 and 98%.

Uccelli et al. evaluated enucleations and central pancreatectomies in 22 patients and did not detect recurrence or death over a short-term follow-up period[24]. Median tumor size in this cohort was 13mm for enucleations and 30mm for central pancreatectomies. Liu et al. found equivalent long-term outcomes for PSR and oncologic resections in PNETs <2cm[29]. A wide range of tumor size cut-offs have been proposed in previous studies[8,29,30]. In this large patient cohort there was no difference in long-term outcomes for PSR or oncologic resections for patients with PNETs < 2cm, as well as those 2–3cm. Our data supports PSR in patients with non-functioning sporadic PNETs smaller than 3cm.

The likelihood of lymph node metastasis in PNETs increases with size. A recent study reported on 210 sporadic PNETs <2cm[31]. Median tumor size in this study was 15mm and parenchyma-sparing procedures were performed in 42% of the patients. Lymph nodes were harvested in 136 of 210 patients and only 10.6% of patients with harvested lymph nodes had lymph node metastasis.

Recurrence rates are high in lymph node positive patients but remain low in node negative patients with small tumors[32]. In our study, lymph nodes were harvested in 88.2% of patients undergoing oncologic resections, but in only 40.2% of PSR patients. However, the rate of patients with positive lymph nodes was equivalent in both groups (PSR 6.7% vs. oncologic resection 7.7%) and DFS and OS were similar for both resection types. Irrespective of resection type, patients with positive lymph nodes experienced reduced DFS and OS. Only patients with positive lymph nodes experienced reduced DFS and OS, while those with negative lymph nodes and no lymph nodes resected had equivalent long- term outcomes. Standard lymphadenectomy in all patients with non-functional PNETs smaller than 3cm does not appear to improve long-term outcomes. Instead, careful patient selection for lymph node-sparing resections can help reduce short and long term postoperative morbidity without impairing long-term outcomes in selected patients. Reviewing preoperative imaging for suspicious lymph nodes and performing endoscopic ultrasound guided FNA can help to determine nodal status prior to an operation in patients with small PNETs[33]. Lymph node-sparing procedures should be considered in patients without suspicious lymph nodes on imaging or high-risk features on endoscopic ultrasound guided FNA.

We demonstrated equivalent disease-free and overall survival for patients undergoing PSR and oncologic resections. Patients who had oncologic resections had higher rates of grade 2–3 tumors, stage T3–4, perineural and lymphovascular invasion. Detailed data on preoperative factors for treatment decision making was unfortunately not available from the registry database. An important requirement for PSR at all centers was the absence of suspicious lymph nodes on pre operative imaging and intra operative evaluation. Despite a higher proportion of high risk pathologic features in patients who had oncologic resections, long-term outcomes did not differ for parenchyma-sparing procedures as compared to oncologic resections.

Our study demonstrated favorable results for PSR in terms of intraoperative blood loss and operative times, however, central pancreatectomies were associated with increased postoperative morbidity, mainly pancreatic fistulas as compared to oncologic resections. Previous studies have shown conflicting results of PSR-related morbidity ranging from

high pancreas-specific complications to low overall morbidity[10,25,28,29,34]. Hüttner et al. performed a meta-analysis of 22 observational studies reporting on oncologic resections and PSR in PNET[35]. The authors found less blood loss, shorter operative times, and shorter hospital stay in PSR patients and similar rates of postoperative morbidity and mortality for both groups. Heterogeneous results of previous studies may be explained by the different morbidity profiles and varying proportions of enucleations and central pancreatectomies. Our study demonstrated higher postoperative complications rates as well as higher POPF and PPH rates, especially for central pancreatectomies as it involves two pancreatic transection planes in a soft pancreas. Other studies confirmed postoperative morbidity of 54–62% and POPF rates of more than 25% in central pancreatectomies[36–39]. We therefore recommend carefully weighing postoperative morbidity rates against pancreatic gland preservation when considering patients for central pancreatectomies.

A limitation of this study is its retrospective nature potentially introducing selection and information bias. However, all data in this study was collected in a prospectively maintained database at four high volume centers with extensive experience in the treatment of pancreatic neuroendocrine tumors. A further limitation of this study is that data on endocrine and exocrine insufficiency after PSR or oncologic resection was not available from the database. Another limitation is the lack of data regarding decision making on parenchyma- and lymph node sparing resection. Preoperative imaging to determine suspicious lymph nodes or local tumor infiltration was unfortunately not available for this study. As a prospective randomized trial is unlikely in this rare tumor entity for PSR, we believe, however, that the current analysis provides meaningful insights and treatment guidance for sporadic PNETs <3cm.

In conclusion, parenchyma-sparing and lymph node-sparing resections are safe in patients with non- functional pancreatic neuroendocrine tumors <3cm. Oncologic resections are associated with higher blood loss, longer operative times, and higher complication rates for similar long-term oncologic outcomes. Parenchyma- and lymph node-sparing resections should be considered for patients with non-functional pancreatic neuroendocrine tumors <3cm amenable to localized resection and no evidence of lymph node involvement or high-risk features.

Acknowledgement

Loeffler Family Foundation funding of PANDA

References

1. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol Off J Eur Soc Med Oncol. 2008;19:1727–1733.
2. Cai L, Michelakos T, Deshpande V, et al. Role of Tumor-Associated Macrophages in the Clinical Course of Pancreatic Neuroendocrine Tumors (PanNETs). Clin Cancer Res Off J Am Assoc Cancer Res. 2019;25:2644–2655.
3. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469–1492. [PubMed: 18703061]

4. Haynes AB, Deshpande V, Ingkakul T, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. Arch Surg Chic Ill 1960. 2011;146:534–538.
5. Zandee WT, de Herder WW. The Evolution of Neuroendocrine Tumor Treatment Reflected by ENETS Guidelines. Neuroendocrinology. 2018;106:357–365. [PubMed: 29320780]
6. Sadot E, Reidy-Lagunes DL, Tang LH, et al. Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study. Ann Surg Oncol. 2016;23:1361–1370. [PubMed: 26597365]
7. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. J Clin Endocrinol Metab. 2013;98:4784–4789. [PubMed: 24057286]
8. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non- Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103:153–171. [PubMed: 26742109]
9. Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. Pancreas. 2020;49:863–881. [PubMed: 32675783]
10. Beger HG. Benign Tumors of the Pancreas-Radical Surgery Versus Parenchyma-Sparing Local Resection-the Challenge Facing Surgeons. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2018;22:562–566.
11. Pea A, Tanno L, Nykänen T, et al. Comparison of Oncological and Surgical Outcomes Between Formal Pancreatic Resections and Parenchyma-Sparing Resections for Small PanNETs (<2 cm): Pancreas2000 Research and Educational Program (Course 9) Study Protocol. Front Med. 2020;7:559–559.
12. Rindi G Nomenclature and classification of neuroendocrine neoplasms of the digestive system. WHO Classif Tumours Dig Syst. 2010;13–14.
13. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg. 2007;246:52–60. [PubMed: 17592291]
14. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA Cancer J Clin. 2017;67:93–99. [PubMed: 28094848]
15. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161:584–591. [PubMed: 28040257]
16. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH)–an international study group of pancreatic surgery (ISGPS) definition. Surgery. 2007;142:20–25. [PubMed: 17629996]
17. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–768. [PubMed: 17981197]
18. Van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw. 2011;45:1–67.
19. Landoni L, Marchegiani G, Pollini T, et al. The Evolution of Surgical Strategies for Pancreatic Neuroendocrine Tumors (Pan-NENs): Time-trend and Outcome Analysis From 587 Consecutive Resections at a High-volume Institution. Ann Surg. 2019;269:725–732. [PubMed: 29189384]
20. Zhang R-C, Ma J, Mou Y-P, et al. Short- and Long-Term Outcomes of Laparoscopic Organ-Sparing Resection for Pancreatic Neuroendocrine Neoplasms. World J Surg. 2020;44:3795–3800. [PubMed: 32700111]
21. Partelli S, Ramage JK, Massironi S, et al. Management of Asymptomatic Sporadic Nonfunctioning Pancreatic Neuroendocrine Neoplasms (ASPEN) ≤2 cm: Study Protocol for a Prospective Observational Study. Front Med. 2020;7:1009.
22. Cherif R, Gaujoux S, Couvelard A, et al. Parenchyma-sparing resections for pancreatic neuroendocrine tumors. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2012;16:2045–2055.

23. Mauriello C, Napolitano S, Gambardella C, et al. Conservative management and parenchyma-sparing resections of pancreatic neuroendocrine tumors: Literature review. Int J Surg Lond Engl. 2015;21 Suppl 1:S10–14.
24. Uccelli F, Gavazzi F, Capretti G, et al. Parenchyma-sparing surgery for pancreatic endocrine tumors. Updat Surg. 2016;68:313–319.
25. Mintziras I, Keck T, Werner J, et al. Indications for resection and perioperative outcomes of surgery for pancreatic neuroendocrine neoplasms in Germany: an analysis of the prospective DGAV StuDoQ|Pancreas registry. Surg Today. 2019;49:1013–1021. [PubMed: 31240463]
26. Cienfuegos JA, Rotellar F, Salguero J, et al. A single institution's 21-year experience with surgically resected pancreatic neuroendocrine tumors: an analysis of survival and prognostic factors. Rev Espanola Enfermedades Dig Organo Of Soc Espanola Patol Dig. 2016;108:689–696.
27. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. Br J Surg. 2014;101:1405–1412. [PubMed: 25132004]
28. Cherif R, Gaujoux S, Couvelard A, et al. Parenchyma-sparing resections for pancreatic neuroendocrine tumors. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2012;16:2045–2055.
29. Liu X, Chin W, Pan C, et al. Risk of malignancy and prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors. Gland Surg. 2021;10:219–232. [PubMed: 33633978]
30. Lindner K, Binte D, Hoeppner J, et al. Resection of Non-Functional Pancreatic Neuroendocrine Neoplasms-A Single-Center Retrospective Outcome Analysis. Curr Oncol Tor Ont. 2021;28:3071–3080.
31. Sallinen VJ, Le Large TYS, Tieftrunk E, et al. Prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study. HPB. 2018;20:251–259. [PubMed: 28988702]
32. Pulvirenti A, Javed AA, Landoni L, et al. Multi-institutional Development and External Validation of a Nomogram to Predict Recurrence After Curative Resection of Pancreatic Neuroendocrine Tumors. Ann Surg. 2021;274:1051–1057. [PubMed: 31567347]
33. Javed AA, Pulvirenti A, Razi S, et al. Grading Pancreatic Neuroendocrine Tumors via Endoscopic Ultrasound-guided Fine Needle Aspiration: A Multi-Institutional Study. Ann Surg. Epub ahead of print January 25, 2022. DOI: 10.1097/SLA.0000000000005390.
34. Wolk S, Distler M, Kersting S, et al. Evaluation of central pancreatectomy and pancreatic enucleation as pancreatic resections--A comparison. Int J Surg Lond Engl. 2015;22:118–124.
35. Hüttner FJ, Koessler-Ebs J, Hackert T, et al. Meta-analysis of surgical outcome after enucleation versus standard resection for pancreatic neoplasms. Br J Surg. 2015;102:1026–1036. [PubMed: 26041666]
36. Paiella S, De Pastena M, Faustini F, et al. Central pancreatectomy for benign or low-grade malignant pancreatic lesions - A single-center retrospective analysis of 116 cases. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2019;45:788–792.
37. Dumitrascu T, Barbu ST, Purnichescu-Purtan R, et al. Risk factors for surgical complications after central pancreatectomy. Hepatogastroenterology. 2012;59:592–598. [PubMed: 22353528]
38. Crippa S, Bassi C, Warshaw AL, et al. Middle pancreatectomy: indications, short- and long-term operative outcomes. Ann Surg. 2007;246:69–76. [PubMed: 17592293]
39. Hank T, Sandini M, Ferrone CR, et al. Association Between Pancreatic Fistula and Long-term Survival in the Era of Neoadjuvant Chemotherapy. JAMA Surg. 2019;154:943–951. [PubMed: 31411659]

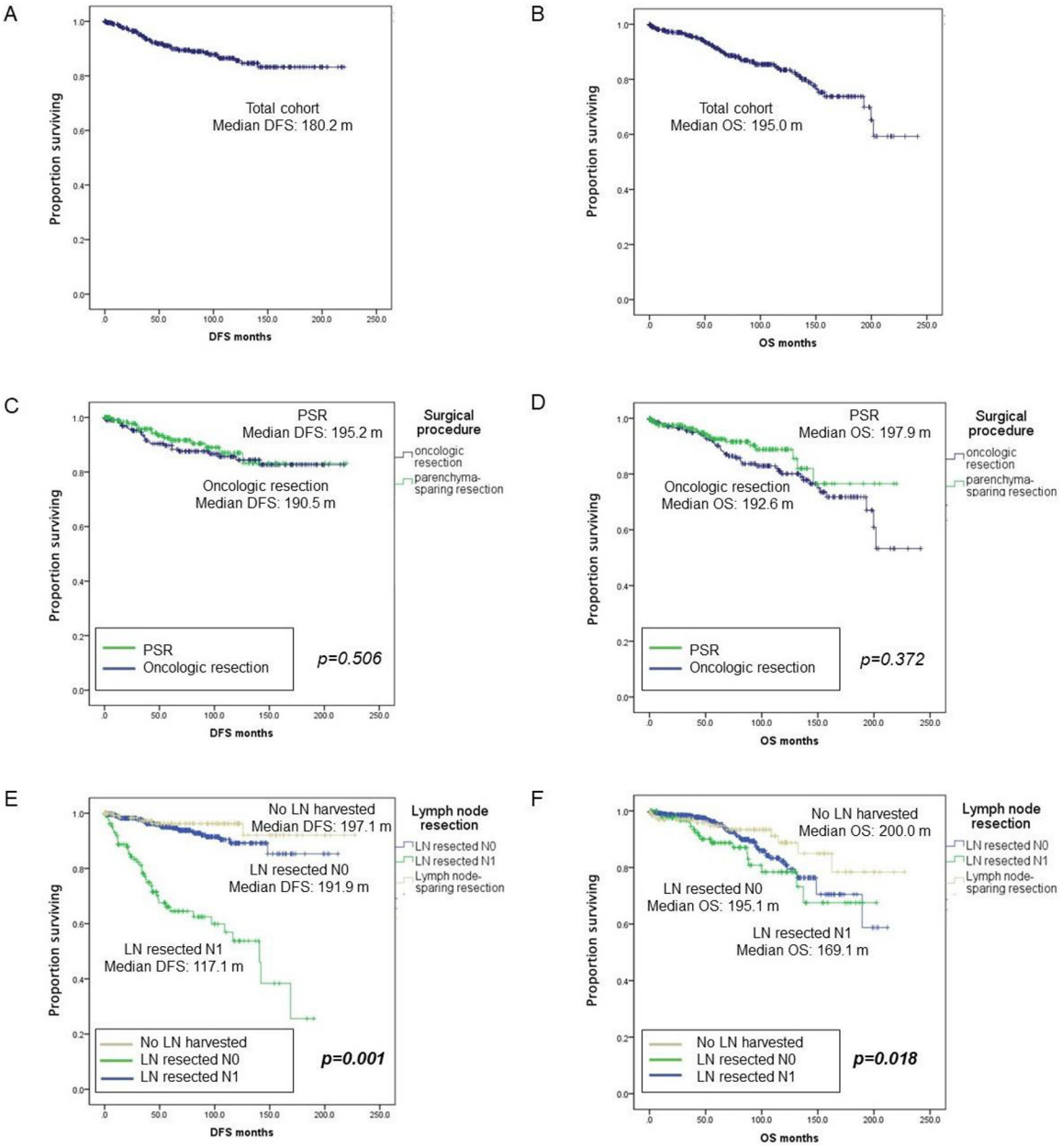

Figure 1.

Disease-free-survival in patients undergoing oncologic resections versus parenchyma-sparing resections and no lymph node resection versus lymph node resections

PSR: Parenchyma-sparing resection, LN: lymph node; DFS: Disease-free survival; OS: Overall survival

Table 1

Baseline, operative and histopathological parameters of patients who underwent parenchyma- sparing resections versus oncologic resections

Baseline and Operative Parameters				
	Total cohort	**PSR**	**Oncologic resection**	
Total n	810 (100.0)	221 (27.3)	589 (72.7)	
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Age in years	59 (0.90)	55 (0.95)	53 (0.91)	0.731
Gender				
Female	392 (48.4)	110 (49.8)	282 (47.9)	0.618
ASA score				
III-IV	352 (43.4)	93 (43.9)	259 (44.0)	0.999
BMI in kg/m2	30.4 (1.13)	30.3 (0.7)	30.5 (1.22)	0.208
Minimal invasive procedures	296 (36.5)	72 (32.6)	224 (38.0)	0.29
Blood loss (ml)	374.3 (29.3)	209.1 (24.8)	411.2 (30.3)	**<0.001**
Operative time(min)	259.0 (7.2)	180 (8.3)	272.6 (6.3)	**<0.001**
Histopathological parameters				
WHO Grading				
G1	626 (77.3)	192 (86.8)	434 (73.7)	
G2	168 (20.8)	28 (12.7)	140 (23.8)	
G3	16 (1.9)	1 (0.4)	15 (2.5)	**<0.001**
Ki-67 Index				
>3	195 (24.1)	29 (13.1)	166 (28.5)	**0.002**
Vascular invasion	155 (19.3)	28 (13.9)	127 (21.6)	**0.011**
Perineural invasion	168 (20.7)	18 (8.9)	150 (25.5)	**<0.001**
Lymph nodes harvested				
Yes	674 (83.3)	111 (40.2)	550 (93.4)	**<0.001**
Number of lymph nodes harvested	11.9 (0.3)	1.4 (0.2)	14.0 (0.4)	**<0.001**
Lymph nodes positive	0.9 (0.07)	0.9 (0.09)	1.59 (0.07)	0.127
Positive nodal status	128 (15.8)	15 (18.5)	113 (19.2)	0.988
T stage (AJCC 8th ed.)				
T3–4	126 (15.4)	19 (8.6)	107 (18.1)	**0.049**
R status				
R+	95 (11.7)	58 (26.2)	37 (6.3)	**<0.001**

PSR: Parenchyma-sparing resection; ASA: American Society of Anesthesiologists; BMI: Body mass index

Table 2

Baseline and operative parameters of matched patients who underwent parenchyma-sparing resections versus oncologic resections

Baseline and Operative Parameters			
	PSR	**Oncologic resection**	
Total n	221 (50.0)	221 (50.0)	
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Age in years	55 (0.95)	55 (0.99)	0.842
Gender			
Female	110 (49.8)	106 (48.0)	0.775
ASA score			
III-IV	93 (43.9)	101 (45.7)	**0.419**
BMI in kg/m2	30.3 (0.7)	29.2 (1.65)	0.555
Minimal invasive procedures	72 (32.6)	30 (13.6)	**<0.001**
Blood loss in ml	209.1 (24.8)	511.2 (37.4)	**<0.001**
Operative time in min	180.0 (8.3)	330.0 (23.2)	**<0.001**
Tumor size in cm	2.1 (0.10)	2.1 (0.11)	0.999
Histopathological parameters			
WHO Grading			
G1	192 (86.8)	169 (76.4)	
G2	28 (12.7)	48 (21.7)	
G3	1 (0.4)	4 (1.9)	**<0.001**
Ki-67 Index			
>3	29 (13.1)	41 (18.6))	**<0.001**
Vascular invasion	28 (13.9)	41 (20.9)	0.065
Perineural invasion	18 (8.9)	42 (21.8)	**<0.001**
Lymph nodes harvested			
Yes	111 (40.2)	195 (88.2)	**<0.001**
Number of lymph nodes harvested	1.4 (0.2)	9.9 (0.6)	**<0.001**
Lymph nodes positive	0.9 (0.09)	1.1 (0.08)	0.808
Positive nodal status	15 (6.7)	17 (7.7)	0.999
T stage (AJCC 8th ed.)			
T3–4	19 (8.6)	44 (20.4)	**<0.001**
R status			
R+	58 (26.2)	18 (8.1)	**<0.001**

PSR: Parenchyma-sparing resection; ASA: American Society of Anesthesiologists; BMI: Body mass index

Table 3

R status, lymph node status and overall survival

Univariate analysis				
	Median OS	**HR**	**95%Cl (lower, upper)**	**p-value**
Total cohort, N0 (n=410)				
R Status				
R0	208.6			
R+	201.8	1.654	0.191, 4.321	0.648
Parenchyma-sparing resections, N0 (n=66)				
R Status				
R0	141.2			
R+	120.5	2.464	0.223, 7.121	0.462

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval

Table 4

Postoperative morbidity in enucleations vs. oncologic resections and central pancreatectomies vs. oncologic resections

Postoperative complications			
	Oncologic resections	**Enucleations**	
Total n	221	121	
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Postoperative complications			
No	136 (61.5)	62 (51.6)	
Yes	85 (38.5)	59 (48.4)	0.087
Clavien Dindo Classification			
0-IIB	195 (88.2)	97 (81.0)	
IIIA-IVB	26 (11.8)	23 (19.0)	0.077
POPF grade B/C	18 (8.1)	26 (21.3)	0.098
DGE	6 (2.7)	5 (4.1)	0.313
PPH	0 (0.0)	1 (0.8)	0.876
Reoperation	1 (0.5)	0 (0.0)	0.999
Postoperative			
30 day mortality	1 (0.5)	0 (0.0)	0.999
Length of stay (days)	7.3 (5.7)	7.5 (8.1)	0.832
Readmission within 30 days	46 (20.1)	24 (19.8)	0.134
	Oncologic resections	**Central pancreatectomies**	
Total n	221	100	
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Postoperative complications			
No	136 (61.5)	43 (43.4)	
Yes	85 (38.5)	56 (56.6)	**0.003**
Clavien Dindo Classification			
0-IIB	195 (88.2)	80 (80.8)	
IIIA-IVB	26 (11.8)	19 (19.2)	**0.044**
POPF grade B/C	18 (8.1)	20 (20.2)	**0.032**
DGE	6 (2.7)	4 (4.0)	0.244
PPH	0 (0.0)	5 (5.1)	**0.021**
Reoperation	1 (0.5)	4 (4.0)	**0.033**
Postoperative			
30 day mortality	1 (0.5)	1 (1.1)	0.524
Length of stay (days)	7.3 (5.7)	7.9 (4.8)	0.252
Readmission within 30 days	46 (20.1)	23 (23.0)	0.305

POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying; PPH: Postoperative pancreatic hemorrhage

Table 5

Lymph-node-sparing resections versus lymph node dissection: Baseline and operative parameters and morbidity

	No Lymph Nodes resected	**Lymph node dissection, N0**	**Lymph node dissection, N+**	
Total n	136 (16.8)	546 (67.4)	128 (15.8)	
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Age in years	56.2 (1.1)	58.8 (0.5)	59.1 (1.1)	0.065
Sex				
Female	66 (48.5)	72 (56.3)	250 (45.8)	
Male	70 (51.5)	56 (43.7)	296 (54.2)	0.102
BMI in kg/m2	30.8 (0.6)	29.5 (0.9)	29.0 (0.9)	0.311
Tumor Site				
Head	17 (12.5)	185 (33.9)	86 (67.2)	**<0.001**
Tail/body	114 (83.8)	354 (64.8)	42 (32.8)	
Complete pancreas	5 (3.7)	7 (1.3)	0 (0.0)	
Operative parameters				
Parameter	n(%)/mean (SE)	n(%)/mean (SE)	n(%)/mean (SE)	p-value
Minimal invasive	210 (38.5)	32 (25.0)	59 (43.4)	**0.005**
procedures Blood loss (ml)	225.1 (1.2)	378.9 (2.2)	471.4 (1.5)	**<0.001**
Operative time (min)	177.7 (1.7)	262.3 (1.4)	297.5 (1.3)	**<0.001**
Postoperative complications				
Postoperative complications				
No	82 (60.3)	256 (56.9)	55 (43.0)	
Yes	54 (39.7)	290 (53.1)	73 (47.0)	**0.008**
POPF grade B/C	20 (14.7)	100 (18.3)	18 (14.0)	0.183
DGE	2 (2.4)	50 (12.9)	13 (14.4)	**0.018**
PPH	2 (4.0)	4 (2.9)	3 (8.6)	0.304
Reoperation	1 (0.7)	10 (1.8)	4 (3.1)	0.354
30 day mortality	1 (0.7)	2 (0.4)	0 (0.0)	0.999
Length of stay (days)	7.8 (7.5)	7.3 (4.1)	6.7 (2.7)	0.362
30 day morbidity	10 (7.3)	33 (6.0)	6 (4.6)	0.446

BMI: Body mass index; POPF: Postoperative pancreatic fistula; DGE: Delayed gastric emptying; PPH: Postoperative pancreatic hemorrhage