Short- and long-term outcomes of laparoscopic organ-sparing resection for pancreatic neuroendocrine neoplasms

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Research article

Keywords: Organ-sparing, Pancreatic neuroendocrine neoplasms, Laparoscopy, Pancreatectomy

Posted Date: July 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27080/v2

Version of Record: A version of this preprint was published at World Journal of Surgery on July 22nd, 2020. See the published version at https://doi.org/10.1007/s00268-020-05707-8.

Abstract

Background: Pancreatic neuroendocrine neoplasms (PNENs) are rare neoplasms associated with a long life expectancy after resection. In this setting, patients may benefit from laparoscopic organ-sparing resection. Studies of laparoscopic organ-sparing resection for PNENs are limited. The aim of this study was to evaluate the short- and long-term outcomes of laparoscopic organ-sparing resection for PNENs.

Methods: A retrospective study was performed for patients with PNENs who underwent laparoscopic organ-sparing pancreatectomy between March 2005 and May 2018. The patients' demographic data, operative results, pathological reports, hospital courses and morbidity, mortality, and follow-up data (until August 2018) were analysed.

Results: Thirty-five patients were included in the final analysis. There were 9 male and 26 female patients, with a median age of 46 years (range, 25-75 years). The mean BMI was 24.6±3.3 kg/m^2. Nine patients received laparoscopic enucleation (LE), 20 received laparoscopic spleen-preserving distal pancreatectomy (LSPDP), and 6 received laparoscopic central pancreatectomy. The operative time, intraoperative blood loss, transfusion rate, and postoperative hospital stay were 186.4±60.2 min, 165±73.0 ml, 0 d, and 9 d (range, 5-23 d), respectively. The morbidity rate, grade ≥III complication rate and grade ≥B pancreatic fistula rate were 34.2%, 11.4%, and 8.7%, respectively, with no mortality. The rate of follow-up was 94.3%, and the median follow-up time was 55 months (range, 3-158 months). One patient developed recurrence 36 months after LE and was managed with surgical resection. The other patients survived without metastases or recurrence during the follow-up. One patient had diabetes after laparoscopic spleen-preserving distal pancreatectomy, and no patients had symptoms of pancreatic exocrine insufficiency.

Conclusions: Laparoscopic organ-sparing resection for selected cases of PNENs is safe and feasible and has favourable short- and long-term outcomes.

Background

Pancreatic neuroendocrine neoplasms (PNENs) are rare tumours that represent approximately 2-4% of pancreatic tumours and have an incidence of 1 per 100,000 population[1, 2]. Due to the availability of high-resolution medical imaging and histopathological methods, the diagnosis of PNENs has increased [3]. PNENs comprise a heterogeneous group of tumours with very varied biological behaviours. Complete surgical resection is the curative modality for resectable PNENs with the goal of long-term survival[3].

Organ-sparing pancreatectomy represents a limited resection alternative to pancreaticoduodenectomy (PD) and distal pancreatectomy (DP) for the treatment of benign or low-grade malignant tumours of the pancreas[4-6]. This procedure is thought to be associated with minimal exocrine and/or endocrine insufficiency, good quality of life, and preservation of the spleen and its immunologic properties [4-6]. Laparoscopic pancreatic surgery has been gaining popularity in the last decade due to recent technological developments in laparoscopic techniques and instruments. Therefore, laparoscopic organ-sparing pancreatectomy is thought to be an ideal procedure for PNENs.

Previous studies of laparoscopic pancreatectomy for PNENs have found advantages related to minimal-access surgery and a good overall disease-specific long-term prognosis[7-9]. Studies of laparoscopic organ-sparing resection for PNENs are limited[9,10]. The aim of this study was to evaluate the short- and long-term outcomes of laparoscopic organ-sparing resection for PNENs.

Methods

Between March 2005 and May 2018, patients with PNENs who underwent laparoscopic organ-sparing pancreatectomy in our institution were reviewed. The preoperative assessment included a computed tomographic (CT) scan, pancreatic magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) or fine-needle aspiration (FNA). The preoperative anaesthesia evaluation was performed using the American Society of Anesthesiology guidelines.

Preoperative, operative, and postoperative data were prospectively collected and retrospectively analysed. The data included patients' demographics, clinical presentations, intraoperative variables (type of resection, operative time, estimated blood loss (EBL), conversion to open surgery, blood transfusion requirement), postoperative hospital stay, morbidity and mortality (within 30 days from surgery), readmission rate (within 30 days from hospital discharge), pathologic findings, and long-term follow-up.

Pancreatic fistula (PF) was assessed according to the International Study Group on Pancreatic Fistula recommendations [11]. Postoperative morbidity was graded using the Clavien-Dindo classification[12]. Grades I and II were grouped as minor, and grades III-V were considered major complications [12].

Patients were followed via outpatient examination. The final follow-up was performed in August 2018. Recurrence or distant metastasis was diagnosed pathologically by surgical resection, biopsy, or cytology and/or radiological examination. Pancreatic endocrine insufficiency was defined as new-onset diabetes mellitus and worsening DM[13]. Subjective pancreatic exocrine function was evaluated via a questionnaire, including questions about the incidence of abdominal discomfort, the presence of diarrhoea and steatorrhea, the intolerance to fat, weight loss and the consumption of pancreatic enzyme supplementation[13].

The Institutional Review Board of Zhejiang Provincial People's Hospital approved this study protocol.

Operative technique

The indications for surgery were discussed by a multidisciplinary team board. The type of pancreatic resection was based on the locations and size of the tumors. Laparoscopic enucleation (LE) was performed for the tumours located ≥3 mm distal from the Wirsung duct (WD)[9]. Laparoscopic central pancreatectomy (LCP) was performed for tumours located in the neck-body of the pancreas < 3 mm from the WD, which allowed 5 cm of the tail of the pancreas to be preserved[9]. When the remaining tissue of the distal pancreas was fibrotic or atrophic or <5 cm long, laparoscopic spleen-preserving distal

pancreatectomy (LSPDP) was performed[9]. LSPDP was performed for tumours located <3 cm from the distal end of the pancreas and <3 mm from the WD[9].

The procedures were planned before surgery, but the final procedure was decided on during surgery based on a combination of macroscopic and intraoperative ultrasonographic findings as well as intraoperative frozen section examination results.

Patients were placed in the supine position with the head slightly elevated. The surgeon and the second assistant who held the laparoscope stood on the right side of the patient, and the first assistant stood on the left side. Five trocars (three 5-mm trocars and two 10/12-mm trocars) were used, and the five trocars were arranged in a V shape[14-18].

Laparoscopic Enucleation, Laparoscopic Spleen-Preserving Distal Pancreatectomy, Laparoscopic Central Pancreatectomy

The surgical techniques for LE, LSPDP, and LCP have been previously described in detail elsewhere [1][14-18].

Histopathological data

Histopathological data, such as tumour size, tumour location, margin status, and lymph node status, were also analysed. Tumours were reviewed and graded based on the mitotic count and Ki-67 index, according to the World Health Organization (WHO) classification[19] and the European Neuroendocrine Tumor Society (ENETS) TNM classification[20].

Statistical analysis

Continuous clinicopathological data were expressed as the mean±standard deviation or median (range) as appropriate. Categorical variables were reported as numbers and percentages. All statistical analyses were performed using SPSS version 19.0.

Results

From March 2005 to May 2018, a total of 35 patients with PNENs underwent laparoscopic organ-sparing pancreatectomy. The demographic variables of the 35 patients are provided in Table 1. There were 9 male and 26 female patients, with a median age of 46 years (range, 25-75 years). The mean BMI was 24.6±3.3 kg/m^2. Four patients underwent previous laparotomy: two underwent cholecystectomy, one appendectomy, and one partial gastrectomy. Of the 35 patients, 10 (28.6%) had functional tumours. All of them were insulinomas. The remaining 25 patients (71.4%) had nonfunctional tumours.

Various preoperative diagnostic tools were used. CT scanning was performed in 35 cases, localizing the tumour in 33 cases. MRI scanning was performed in 23 cases, localizing the tumour in 22 cases. EUS

was performed in 15 cases, localizing the tumour in 15 cases. In 15 cases, preoperative cytology was performed using FNA.

Nine tumours (25.7%) were located in the pancreatic head and neck: there was 1 case of 2 lesions, and 16 (45.7%) were located in the body while 10 (28.6%) were located in the tail of the pancreas. Nine LE (25.7%), 6 LCP (17.2%) and 20 LSPDP (57.1%) procedures were performed: 16 with the Kimura technique and 4 with the Warshaw technique. Combined resection of adjacent organs was performed in four patients. Concomitant cholecystectomy was performed in three patients, and partial gastrectomy was performed in one patient. No patients were converted to open surgery.

The postoperative data are provided in Table 2. The mean operating time was 186.4±60.2 min, and the mean EBL was 165±73.0 ml. The first flatus time, diet start time and postoperative hospital stay were 2.1±1.1 d, 3 d (range, 1-7 d), and 9 d (range, 5-23 d), respectively. There was no postoperative 30-day mortality. Postoperative complications occurred in 12 patients (34.2%). According to the Clavien-Dindo classification, most complications were classified as grade Ⅱ or Ⅲ. Grade ≥Ⅲ complications occurred in 4 patients (11.4%). Of the 35 patients, 3 patients (8.7%) developed grade B PF, and no patients developed grade C PF. Two patients required percutaneous drainage, and 1 patient had persisted peripancreatic drainage for 4 weeks. Two patients (5.8%) developed haemorrhage. One patient experienced bleeding of the splenic artery pseudoaneurysm after LSPDP (Kimura technique) and underwent splenic arterial embolization to achieve haemostasis. Another patient experienced bleeding of the gastroduodenal artery (GDA) after LCP and underwent GDA embolization and laparoscopy evacuation of the hematoma.

The histopathological data are provided in Table 3. The mean tumour diameter was 2.2±1.5 cm. According to the WHO classification[19], 24 patients (68.6%) were graded G1 and 11 patients (31.4%) G2, while no patients were graded G3. According to the ENETS TNM classification [20], 20 patients (57.1%) were stage I, 13 patients (37.1%) were IIA, and 2 patients (5.8%) were IIIA. All patients had R0 status.

A total of 33 patients (follow-up rate 94.3%) were followed via outpatient examination. The median follow-up period was 55 months (range 3–158 months). One patient developed recurrence 36 months after LE. Tumour recurrence occurred in the pancreatic body and head. The patient received DP and enucleation of the tumour in the pancreatic head. The other patients survived without metastases or recurrence during the follow-up. One patient experienced intestinal obstruction 2 years after LSPDP. One patient developed new-onset diabetes and was treated with oral drugs after LSPDP. No patients had symptoms of pancreatic exocrine insufficiency.Three patients who underwent LSPDP with the Warshaw technique were followed. One patient developed collateral venous vessels around the gastric fundus and reserved spleen but no clinically relevant symptoms, such as variceal bleeding. Sixteen patients who underwent LSPDP with the Kimura technique were followed. Normal patency of the splenic artery and vein was observed in 14 and 14 patients within 1 month of surgery and in 15 and 14 patients 6 months or more after the operation, respectively. Two patients eventually developed collateral venous vessels around the gastric fundus and reserved spleen, with one case of variceal bleeding.

Discussion

Laparoscopic organ-sparing resection for PNENs was initially described by Gagner in 1996 [21]. The patient underwent LE for an insulinoma in the anterior body of the pancreas in 3 hours, and the hospital stay was 4 days. No recurrence was seen upon follow-up. Owing to the complicated operation and low prevalence of PNENs, papers about laparoscopic organ-sparing resection for PNENs reported in the literature are limited[9,10]. Cienfuegos et al[9] documented the effectiveness of laparoscopic organ-sparing resection in selected cases of PNENs. However, their study also included 11 cases of laparoscopic radical distal pancreatosplenectomy for PNENs[9]. Moekotte et al[10] performed 87 cases of LSPDP for PNENs with feasible short-term outcomes. However, their study also included 142 cases of LSPDP for pathologies other than PNENs and without long-term outcomes[10]. To the best of our knowledge, this study focused only on laparoscopic organ-sparing resection for PNENs. Our study demonstrated that laparoscopic organ-sparing resection for selected cases of PNENs is safe and feasible and has favourable short- and long-term outcomes.

The morbidity rates of laparoscopic pancreatectomy for PNENs reported in the literature varies greatly from 21.5% to 50%[8, 9]. PF is the most frequent complication after laparoscopic pancreatectomy for PNENs. The PF rates vary greatly from 21.5% to 36.1% [8, 9]. These studies include both laparoscopic organ-sparing resection and standard resection. Cherif et al[22] reported a high rate of morbidity (76%) and PF (grades B and C) (42%) after open parenchyma-sparing resection for PNENs. The present study revealed that postoperative complications occurred in 12 patients (34.2%) and PF in 3 patients (8.7%, grade B). The present study used the new version of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula[11]. Our pilot studies showed that the morbidity rates and PF rates of LE, LSPDP and LCP were similar to those of open surgery[14,15,16,18]. Therefore, we believe that it is not the type of technique (laparoscopic or open) but the patient's condition and the operation's difficulty level that are associated with PF formation.

The methods of PD or DP, which sacrifice the pancreatic parenchyma and spleen, lead to endocrine and exocrine deficiency, the possibility of overwhelming post-splenectomy infection (OPSI) and a potential increased risk of malignancy. Hence, organ-sparing pancreatectomy has increasingly become an option to treat benign or low-grade malignant tumours to preserve the pancreatic parenchyma and spleen as much as possible. Zhang et al[14,15,18]reported that LE, LSPDP and LCP are safe and feasible for benign or borderline malignant lesions with a faster recovery. LCP is associated with better quality of life[18]. Choi et al[23] confirmed that LSPDP was associated with better quality of life than laparoscopic distal pancreatectomy (LDP) with splenectomy. Song et al[24] reported that 2 (8%) and 10 (38.5%) patients had new-onset diabetes and weight loss, respectively. New-onset diabetes was less frequent after LCP than after extended LDP (8% vs. 30.8%, p=0.037) [24]. Cienfuegos et al[9] reported that none of the patients with early-stage PNENs treated with laparoscopic organ-sparing techniques presented with recurrence during a mean follow-up of 51 months. In our study, only one patient developed recurrence 36 months after LE. The other patients survived without metastases or recurrence during the follow-up. One patient developed new-onset diabetes and was treated with oral drugs after LSPDP. No patients had symptoms

of pancreatic exocrine insufficiency. Splenic perfusion was well preserved in all the follow-up patients 6 months or more after the operation. Therefore, laparoscopic organ-sparing pancreatectomy for PNENs has the advantages of minimal access and preservation of function.

Compared to standard resection, laparoscopic organ-sparing pancreatectomy is not optimal in terms of oncologic resection, with limited margins and nonstandard lymphadenectomy procedures. Cherif et al[22] suggested that parenchyma-sparing pancreatectomy should be considered for low-grade tumours suspected to be nonsecreting tumours less than 2 cm in size or insulinoma in the absence of distant or lymph node metastasis on preoperative assessment. Cienfuegos et al[9] regarded tumours with no vascular invasion (stages I (T1N0M0), IIA (T2N0M0) and IIB (T3N0M0) established by the ENETS) as the best candidates for laparoscopic organ-sparing pancreatectomy. In our study, all functional tumours were insulinomas. All tumours were graded G1 or G2, and none were graded G3. Twenty patients (57.1%) were considered stage I, 13 patients (37.1%) IIA, and 2 patients (5.8%)IIIA. Most patients had an excellent overall prognosis. Therefore, more cases are required to evaluate which of the advanced stages of PNENs are suitable for laparoscopic organ-sparing pancreatectomy.

In our study, the mean tumour diameter was 2.2±1.5 cm. Most tumours were less than 2 cm. The challenge was to locate the tumour and make the decision regarding the surgical approach. The planned surgical approach was governed largely by the findings of preoperative localization studies but may have been commonly changed in accordance with the intraoperative findings. During the operation, ultrasonic examination of the pancreas was used to locate neoplasms that were deep in the parenchyma and to ensure the distance between the neoplasm and the main pancreatic duct.

The limitations of this study were its retrospective design with long inclusion period and very low number of included patients per year.The ideal study would be a large, prospective randomized trial, which is difficult to accomplish owing to the infrequent diagnosis of patients with PNENs suitable for laparoscopic organ-sparing pancreatectomy. Despite these limitations, we believe that this study can provide valuable evidence in clinical practice.

Conclusions

Laparoscopic organ-sparing resection for selected cases of PNENs is safe and feasible and has favourable short- and long-term outcomes.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Zhejiang provincial people's Hospital approved this study. The written informed consent was obtained from the patients before inclusion in the study.

Consent for publication

All the authors express the consent for publication on World Journal of Surgical Oncology.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

Ren-Chao Zhang, Jun Ma, Yi-Ping Mou, Yu-Cheng Zhou, Wei-Wei Jin, and Chao Lu have no conflict of interest or financial ties to disclose.

Funding

There were no funding contributions to this study.

Authors' contributions

ZRC and MYP conceived and designed the study. ZRC, MYP and ZYC performed the operation. MJ, JWW and LC collected and analyzed data. ZRC drafted the manuscript. MYP revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements
Not applicable.

Abbreviations

CT: Computed tomographic; DP: Distal pancreatectomy; EBL: estimated blood loss; ENETS :European Neuroendocrine Tumor Society; EUS: Endoscopic ultrasound ; FNA :fine-needle aspiration; LCP: Laparoscopic central pancreatectomy; LE: Laparoscopic enucleation; LSPDP :Laparoscopic spleen-preserving distal pancreatectomy; MRI: Magnetic resonance imaging; PD:Pancreatoduodenectomy; PF :Pancreatic fistula;PNENs: Pancreatic neuroendocrine neoplasms; WD :Wirsung duct; WHO: World Health Organization

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Tables

Table 1

Baseline characteristics

Age (year)	46 (range,25–75)
Gender (Male/Female)	9/26
BMI (kg/m^2)	24.6 ± 3.3
Diabetes preoperative	1(2.9%)
ASA score	
1	8(22.9%)
2	27(77.1%)
Previous laparotomy	4(11.4%)
Type of tumor	
Functional	10(28.6%)
Insulinoma	10(28.6%)
Non-functional	25(71.4%)
Tumor location	
Head-neck	9(25.7%)
Body	16(45.7%)
Tail	10(28.6%)
Type of surgery	
Enucleation	9(25.7%)
Central pancreatectomy	6(17.2%)
Spleen-preserving distal pancreatectomy	20(57.1%)
Data are expressed as mean ± SD or median (range) or n(%).	
SD,standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists.	

Table 2

Surgical Outcomes

Operative outcomes	
Operating time(min)	186.4 ± 60.2
EBL(ml)	165 ± 73.0
Transfused patients	0
Postoperative outcomes	
First flatus time(days)	2.1 ± 1.1
Diet start time(days)	3(range, 1–7)
Postoperative hospital stay (days)	9(range,5–23)
Overall complications	12 (34.2%)
Minor complications (Grade Ⅰ,Ⅱ)	8(22.8%)
Major complications (≥ Grade Ⅲ)	4(11.4%)
Pancreatic fistula	3(8.7%)
Grade B	3(8.7%)
Grade C	0
Bleeding	2(5.8%)
Delayed gastric empty	1(2.9%)
Intra-abdominal infection	2(5.8%)
Reoperation	1(2.9%)
Percutaneous drainage	2(5.8%)
Readmission	0
Mortality	0

Data are expressed as mean ± SD or median (range) or n(%).
EBL, estimated blood loss.

Table 3

Pathologic characteristics

Neoplasm size on histopathology (cm)	2.2 ± 1.5
WHO classification (2010)	
G1	24(68.6%)
G2	11(31.4%)
G3	0
Tumor stage (TNM)	
I (T1N0M0)	20(57.1%)
IIA(T2N0M0)	13(37.1%)
IIIA (T4N0M0)	2(5.8%)
Negative surgical margin	35(100%)

Data are expressed as mean ± SD or n(%) or unless otherwise specified. World Health Organization,WHO.