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Short- and long-term outcomes of laparoscopic organ-sparing resection in pancreatic neuroendocrine tumors: a single-center experience

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Abstract

Background Laparoscopic organ-sparing pancreatectomy (LOSP) is an ideal therapeutic option in selected cases of pancreatic neuroendocrine tumors (PNETs). Nevertheless, given the low frequency of PNETs, there is scarce evidence regarding short and particularly long-term outcomes of LOSP in this clinical setting.

Methods All patients with PNETs who underwent surgery (under a LOSP policy) were retrospectively reviewed from a prospective database maintained at our center. Preoperative characteristics, operative data, pathological features and postoperative outcomes were analyzed.

Results Between December 2003 and December 2015, 36 patients with PNETs underwent laparoscopic resections. Ten were functional tumors, 26 non-functional and 16 were "incidental" cases. The following procedures were performed: one enucleation, eight central pancreatectomies (LCP), one resection of the uncinate process and 26 distal pancreatectomies (DP) (15 of them laparoscopic vessels-preserving). There were no conversions to open surgery, and no drains were routinely left. Mean operative time was 288 min (SD 99). Hospital stay was 6 days. Eighteen patients (50%) experienced some complication of which most were mild (Clavien–Dindo I/II). Three postoperative bleedings occurred: two grade B/one grade C; two required laparoscopic reoperation. Thirteen (36.1%) patients developed peripancreatic fluid collections: two were symptomatic and were managed with transgastric drainage (one presented post-puncture abscesification requiring surgical drainage and splenectomy). Four patients (11%)—one DP and three LCP—developed new-onset pancreatogenic diabetes mellitus (NODM) in the long term. According to the European Neuroendocrine Tumor Society, 19 cases were stage I, seven IIA, two IIIA, one IIIB and seven stage IV. Over a mean follow-up of 51 months, two patients died, one due to recurrence of the tumor and another due to cirrhosis.

Conclusions The existing different surgical options must be individually considered according to the location and particular characteristics of every tumor. Results from this single-center study document the effectiveness of LOSP in selected cases of PNETs.

Keywords Organ-sparing pancreatectomy · Organ-saving surgery · Neuroendocrine tumor · Pancreas · Laparoscopy

Abbreviations

PNETs	Pancreatic neuroendocrine tumors
LOSP	Laparoscopic organ-sparing pancreatectomy
LCP	Laparoscopic central pancreatectomy

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DP	Distal pancreatectomy
LVPDP	Laparoscopic vessels-preserving distal pancreatectomy
NODM	New-onset pancreatogenic diabetes mellitus
LEN	Enucleation
LDP	Laparoscopic distal pancreatectomy
WD	Wirsung duct
LRDPS	Laparoscopic radical distal pancreatosplenectomy
RAMPS	Radical anterograde modular pancreatosplenectomy
SD	Standard deviation
CT	Multislice computer tomography
MRI	Magnetic resonance imaging
EUS	Endoscopic ultrasound
ENETS	European neuroendocrine society
FNA	Fine-needle aspiration
BMI	Body mass index

Pancreatic neuroendocrine tumors (PNETs) account for 1–2% of all pancreatic tumors and have an incidence of 1 per 100,000 population [1–4]. In recent years, the prevalence of such tumors has increased due to the use of more sensitive imaging techniques [multislice computer tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS)]. Currently, approximately 40% of PNETs are diagnosed incidentally [5–7].

Pancreatic neuroendocrine tumors (PNETs) comprise a heterogeneous group of tumors with a very varied biological behavior, ranging from indolent, well-differentiated tumors to those which are far more aggressive [8–11]. Until 2010, no common criteria for the nomenclature and pathologic staging (TNM) existed, which led to a degree of confusion [12–14].

Since the first laparoscopic resection of a PNET by Gagner in 1994 [15], the number of these procedures has progressively increased, especially over the last decade [16–19]. Nevertheless, given the low prevalence of such tumors and the technical difficulties involved, there are no prospective randomized studies comparing laparoscopic and open techniques nor large series specifically focusing on outcomes of laparoscopy in PNETs. Scientific evidence comes from meta-analyses and systematic reviews which confirm the well-established benefits of laparoscopic techniques in pancreatic resections [20–26].

As PNETs are frequently single, small (mean tumor size: around 3 cm) and well-defined tumors, they are ideal candidates for laparoscopic organ-sparing pancreatectomy (LOSP), i.e., laparoscopic enucleation (LEN), laparoscopic central pancreatectomy (LCP) and resection of the uncinate process. In the same way, benign tumors located in the tail and not amenable to being treated with these techniques can be treated with a spleen-preserving laparoscopic distal pancreatectomy (LDP) preferably with the splenic vessel-preserving techniques (LVPDP) [9, 11, 16, 27].

In contrast, in cases of suspected or confirmed malignancy, techniques designed to ensure the oncological radicality can be performed laparoscopically using the same principles as in open procedures [10, 11, 28, 29].

The aim of the present study is to review a 12-year single-center experience of laparoscopic PNETs resections carried out using organ-sparing techniques.

Materials and methods

Data collection

The databases of University of Navarra Clinic were reviewed to identify patients who had undergone laparoscopic resection of the pancreas for PNETs, between December 2003 and December 2015. Approval for the study was obtained from the Institutional Review Board, and written informed consent was obtained from the participants before inclusion in the study.

Variables with a prospective evaluation were demographic characteristics, clinical presentation, preoperative workup, type of resection, intraoperative data and postoperative course were obtained from a prospective database. Additional clinical data and pathological features were retrospectively obtained from medical records. Patients presenting with symptoms and serum markers of hormone excess were classified as "functional" tumors. Non-functional PNETs were defined as lesions without symptoms related to hormone secretion. Patients were classified as "symptomatic" when clinical symptoms such as weight loss, abdominal pain, new onset of diabetes or bowel abnormalities were present at diagnosis. Incidental PNETs were defined as tumors incidentally discovered in asymptomatic patients who underwent abdominal imaging for unrelated causes.

The preoperative clinical staging was performed by CT and MRI, endoscopic ultrasound (EUS) and fine-needle aspiration (FNA). Cytology "in situ" and immunocytochemistry were performed whenever possible. All operative indications were discussed by a multidisciplinary board that included hepatobiliary surgeons, medical and radiotherapy oncologists, gastroenterologists, abdominal radiologists and pathologists.

Once the indication for surgery was confirmed, the type of pancreatic resection was based on the following anatomic premises. In single tumors with no vascular invasion or adenopathies (stages IA (T1N0M0) and IB (T2 N0M0), located <3 cm from the distal end of the pancreas, LVPDP. In similar tumors (IA, IB) located ≥3 cm from the tail of the pancreas and ≥3 mm distant from the duct of Wirsung (WD), LEN was performed. In similar tumors located in the neck-body of the pancreas <3 mm from the WD and which allowed 5 cm of the tail of the pancreas to be preserved, LCP was performed. When the remaining tissue of the distal pancreas was fibrotic or atrophic or <5 cm long, LVPDP was performed.

In more advanced stages IIA ($T_3N_0M_0$), IIB, III and IV as established by the European Neuroendocrine Tumor Society (ENETS) or AJCC, laparoscopic radical distal pancreaticosplenectomy (LRDPS) were performed [30, 31].

Patients with extrapancreatic disease (stage IV) at the time of diagnosis were seen by a multidisciplinary board regarding the need for adjuvant chemotherapy.

Operative technique

All operative procedures were carried out by or under the supervision of the same surgeon (FR). In all cases, amoxicillin/clavulanic acid was given for antibiotic prophylaxis; somatostatin analog (100 µg/8 h subcutaneously for 7 days) was administered to prevent pancreatic leakage. In patients with an early discharge, this was kept in an outpatient regime. Operative time was defined as the time elapsing between the first incision and skin closure. In most cases, a 5-mm 30° camera was used. All the trocars were of 5 mm except one 12-mm working trocar, through which the ultrasound (US) probe or endo-stapler was inserted. Length of hospital stay was defined as the numbers of days from operation to hospital discharge.

Enucleation

As described, LEN was performed when a sufficient parenchymal thickness (≥3 mm) between the lesion and the main pancreatic duct existed. The technique employed is similar to that described in detail by Fernandez–Cruz et al. [32, 33].

Distal pancreatectomy with preservation of the splenic vessels

All operations were performed with the patient in the lithotomy position with the surgeon positioned between the patient's legs.

A pneumoperitoneum was created (CO_2 at 12 mmHg) with the help of a Veress needle. The supraumbilical 5-mm optic trocar was inserted and then, 3-4 additional trocars were inserted to tailor the resection to the patient's habitus and tumor location [34].

After exploratory laparoscopy had been performed to rule out extrapancreatic disease, a window was created through the gastrocolic ligament for visualization of the lesser sac, taking care not to damage the gastroepiploic arcade and left gastroepiploic vessels. In all cases, laparoscopic US was then performed to confirm tumor location, size, its relation to the WD and the splenic vessels as well as the assessment of the remnant pancreatic parenchyma following resection. This US control helped to define the resection line with a margin of 1 cm, as well as to assess splenic vessel patency after resection.

After freeing the adherences of the posterior wall of the stomach to the pancreas, the body and tail of the pancreas were exposed with a hook, the peritoneum of the lower edge of the pancreas was freed and the artery and splenic/mesenteric vein were identified. A window was created in the fibro-adipose tissue of the inferior edge of the body of the pancreas with the help of an articulating finger-type dissector, and a cotton tape was passed around the pancreas to perform the pancreas hanging maneuver which allowed the pancreas to be separated from the splenic vessels/superior mesenteric vein.

The pancreas was transected by using an endo-stapler with 3.5-/4.8-mm staples (EndoGIA II 60 4.8/3.5) with staple line reinforcement (Gore Seamguard Bioabsorbable Staple Line Reinforcement, W.L. Gore & Associates, Flagstaff, AZ). The pancreas was compressed with the stapler, and the firing was slowly performed, depending on the texture of the gland.

The pancreas was freed from the splenic vessels in a medial to lateral direction using blunt dissection. Once the pancreas was divided, the gland was released from the splenic artery and vein with gentle dissection of the small vessels that were divided preferably between small titanium clips (Horizon, Endoscopic ligating clips. Weck; Teleflex, Limerick. PA) limiting the use of energy devices.

Limited resections: LCP and uncinate resection

The surgical technique for LCP and laparoscopic resection of the uncinate process has been previously described in detail elsewhere [35, 36].

Laparoscopic radical distal pancreatosplenectomy (LRDPS)

LRDPS procedures were performed as a modification of the radical anterograde modular pancreatosplenectomy (RAMPS) technique described by Strassberg and its laparoscopic description by Fernandez–Cruz, while the extent of the lymphadenectomy was tailored to the particular location of the tumor [30, 31, 37].

The specimens were placed in a protective bag and extracted through the 12-mm incision, except in the LRDPS procedures, where a Pfannenstiel incision was made for specimen removal. Routine drainage was not left in pace. All ports larger than 5 mm were closed with fascial sutures. The nasogastric tube was removed at the end of the procedure and liquid tolerance initiated on the first postoperative day.

All patients underwent abdominal ultrasound scans before discharge. Patients were monitored at 1, 6 and 12 months during the first year and then every 6 months as established in the NCCN criteria [12, 38, 39]. Pancreatogenic diabetes was based on the American Diabetes Association Classification [40].

Morbidity was graded according to the Clavien–Dindo classification [41]. Definition of pancreatic fistula, postoperative hemorrhage and delayed gastric emptying was based on the International Study Group of Pancreatic Surgery [42–44].

Histopathological study

The diagnosis of PNETs was based on conventional histology and immunohistochemical findings (chromogranin A, synaptophysin and Ki 67). All cases were reviewed and classified according to the World Health Organization (WHO) criteria, as well as the TNM-based staging system of the ENETS [13, 14, 45–47]. Examination of the resection margins was carried out according to pathology guidelines [12, 38, 46]. Vascular invasion and necrosis were recorded whenever possible.

Statistical analysis

Descriptive statistics included mean, standard deviation (SD), median and range for continuous variables and frequencies for categorical variables. In line with other authors [48, 49], the ENETS staging classification was simplified into four categories: I, II, III and IV [46].

All the analyses were performed using Stata 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Tx: Stata Corp).

Results

From December 2003 to December 2014, 40 patients underwent laparoscopic resection for suspicion of PNETs. Of these 40 patients, four cases were excluded due to the definitive histology: one patient with a peripancreatic paraganglioma, two patients with chronic pancreatitis and ductal ectasia with endocrine hyperplasia, and one patient with renal tumor metastases. Thus, 36 patients were included in the final study.

The demographic data of the patients are shown in Table 1. The mean age was 55.1 years (SD 12.1; range 30–75); all were sporadic and had a mean body mass index (BMI) of 26.2 (SD 5.5; range 17.6–45.8). At the time of diagnosis, six patients were diabetic. Of the 36 patients, 10 cases (27.7%) were functional tumors: seven with insulinoma, one gastrinoma, one vipoma and one carcinoid tumor. The remaining 26 patients (72.2%) were non-functional, of which 18 (50%) were diagnosed incidentally.

In 22 cases (61%), prior cytology was performed using FNA. This was diagnostic in 21 subjects. Preoperative examinations included 21 (58.3%) CT scans, 7 (19.4%) US, 4 (11.1%) MRI scans and three EUS, and in one case PET was used.

One tumor was located in the uncinate process, nine (25%) in the body and 26 (72.2%) in the tail of the pancreas. Eight LCP, one resection of the uncinate process, one EN and 26 DP (72%) were performed: 15 LVPDP and 11 LRDPS.

No patient required conversion to open surgery. Mean operative time was 288 min (SD 99.13; median range 147–515), and the mean hospital stay was 6 days (SD 0.9; range 2–21, median 4 days). Of the 36 patients, 18 (50%) experienced some form of complication, the most frequent of which ($n = 8$, 22%) were Clavien-Dindo grade I (postoperative nausea, Table 2). Three episodes of postoperative intraabdominal bleeding were reported. Two were grade B and one grade C as defined by the international classification [43]. Two of these patients required blood transfusion (transfusion rate 5.5%) and underwent repeat surgery using laparoscopy.

Our strategy of no leaving drains prevents us from specifying the fistula rate as defined by the ISGPF [42]. Of the 36 patients, 13 (36.1%) developed postoperative peripancreatic fluid collections, of which 11 were asymptomatic and were spontaneously reabsorbed. The median diameter of these collections was 4.8 cm (range 2.7–13.7), and they were observed between 3 and 90 days after the operation (median 30 days). Two patients referred abdominal pain in relation to retrogastric fluid collections (maximum diameter 8.7 and 7.7 cm). They were readmitted for transgastric EUS-guided drainage at p.o.d. 20 and 68, respectively. The second of these patients subsequently developed a post-puncture abscess, which required surgical drainage and splenectomy by an open approach. In summary, two patients (5.5%) were readmitted and three patients (8.3%) underwent repeat operations (two postoperative bleedings and one post-transgastric drainage abscesification of fluid collection).

Two patients had complications related to their incisions—infection and trocar site hernia, respectively.

Table 1 Baseline demographic, clinical and surgical characteristics of patients

Age, years, mean (SD)	55.10 (12.1)
Male, *n* (%)	17 (47.2)
BMI, kg/m^2, mean (SD)	26 (5.5)
Diabetes preoperative, *n* (%)	6 (16.6)
ASA grade, *n* (%)	
I	3 (3.8)
II	25 (69.4)
III	8 (22.2)
Type of tumor, *n* (%)	
Functional	10 (27.7)
Insulinoma	7 (70)
Gastrinoma	1 (10)
Vipoma	1 (10)
Carcinoid	1 (10)
Non-functional	26 (72.2)
Incidental	18 850)
Tumor location, *n* (%)	
Head-neck	2 (5.5)
Body	8 (22.2)
Tail	26 (72.2)
Type of surgery, *n* (%)	
Enucleation	1 (2.7)
Uncinate process resection	1 (2.7)
Central pancreatectomy	8 (22.2)
Distal pancreatectomy	26 (72.2)
LVPDP*	15 (57.7)
LRDPS**	11 (42.3)

SD standard deviation, *ASA* American Society of Anesthesiologists physical status classification, *LVPDP** laparoscopic vessels-preserving distal pancreatectomy, *LRDPS*** laparoscopic radical distal pancreatosplenectomy

Four patients (11.1%)—one undergoing distal pancreatectomy and three undergoing central pancreatectomy—developed new-onset diabetes (type IIIc American Diabetes Association; fasting plasma glucose >126 mg) and were treated with metformin [40]. The onset of diabetes occurred between 1 month and 9 years after the operation.

The mean diameter of the tumors was 2.1 cm (SD 1.32; range 0.3–5.7). In four cases (11.1%), the tumors were multicenter. Following the ENETS classification, 19 cases were stage I, seven cases IIA, two tumors IIIA, one case IIIB and seven cases with synchronous liver metastases (stage IV). Vascular invasion was observed in nine (25%) cases, and necrosis in seven (30.4%) of the 30 patients studied (Table 3). Of the 36 patients, resection was curative (R0) in 29 and palliative in seven, who presented synchronous liver metastases; in two cases liver resection was subsequently performed.

With a mean follow-up of 51.05 months (SD 36.7; median 44.4; range 5–183), two patients died: one due to recurrence of the tumor and the other due to liver failure secondary to cirrhosis at 54 and 28 months, respectively. Tumor recurrence occurred in two patients (pancreas and bone). These recurrences took place in patients who had advanced tumors at diagnosis and had undergone LRDPS.

Discussion

Although PNETs comprise a heterogeneous group of tumors whose biological behavior varies greatly, they do exhibit a series of features which make them ideal candidates to be treated by parenchyma-sparing resections of the pancreas carried out laparoscopically. The results herein shown and the fact that none of the patients with early stages PNET treated with parenchymal-sparing techniques presented recurrence during follow-up support the effectiveness of these techniques (and the algorithm shown in Fig. 1) that should be tailored and considered on a case-by-case basis. However, the prevalence of these tumors is low, and the technical exigencies associated with such procedures are considerable.

In our series, the phenotype of the tumors was very similar to that described in large multicenter studies [49–51]. However, it is worth highlighting that a greater number of our tumors were non-functional ($n = 25$; 72.2%) and that 50% of them ($n = 18$) were diagnosed incidentally. This figure is in line with other series where the percentage of incidentally diagnosed tumors has ranged from 35 to 45% and has even reached 80–82% [6, 50, 52, 53].

Given the lack of prospective randomized studies comparing laparoscopic and open distal pancreatectomy, the current clinical evidence is based on data from six systematic reviews and meta-analyses of case–control studies [10, 20, 22, 25, 26, 54–57]. In spite of the heterogeneity of the series, the authors report a significant decrease in the use of blood products, hospital stay, the delay in restoring food intake and intestinal transit and operative morbidity (33.9 vs. 44.02%; OR 0.73, $p = 0.02$) in favor of laparoscopy [10, 26]. In contrast, the incidence of pancreatic fistulas was found to be similar (19.1 vs. 19.9%) as was operative mortality. Only one author reported the frequency of conversions to open surgery, and none of the studies in the meta-analyses provided data on the incidence of postoperative diabetes [54].

Worthy of note is the low number of enucleations (1/36) in our series in comparison with more complex techniques such as splenic vessel-saving central or distal pancreatectomies [58]. Given the requirement for a 3-mm safety margin from the duct of Wirsung, limited anatomic

Table 2 Perioperative outcome

Length hospital stay, days, mean (SD)	6 (0.9)
Duration of surgery, minutes, mean (SD)	287.8 (99.1)
Dindo–Clavien grade*, *n* (%)	
0 (non-complication)	18 (50)
I	8 (22.2)
II	4 (11.1)
IIIa	2 (5.5)
IIIb	2 (5.5)
IVa	1 (2.7)
IVb	1 (2.7)
Post-pancreatectomy hemorrhage grade** overall, *n* (%)	3 (8.3)
B	2 (66.7)
C	1 (33.3)
Intraabdominal infection, *n* (%)	1 (2.8)
Wound infection, *n* (%)	1 (2.8)
Wound dehiscence, *n* (%)	1 (2.8)
New-onset diabetes***, *n* (%)	4 (11.1)
Peripancreatic fluid collections, *n* (%)	13 (36.1)
Asymptomatic	11/13
Symptomatic (abdominal pain)	2/13

* Ref. [41]; ** Ref. [43]; *** Ref. [4]

Table 3 Pathological findings

Tumor diameter size, cm, (SD)	2.05 (1.3)
WHO classification (2010)*, *n* (%)	
G1	25 (69.4)
G2	9 (25)
Unknown	2 (5.6)
ENETS stage (TNM)**, *n* (%)	
I ($T_1N_0M_0$)	19 (58.2)
IIA ($T_2N_0M_0$)	7 (19.4)
IIIA ($T_4N_0M_0$)	2 (5.6)
IIIB ($T_{1–4}N_1M_0$)	1 (2.8)
IV ($T_{1–4\ any}NM_1$)	7 (19.4)
Tumor necrosis, *n* (%)	7 (19.4)
Vascular invasion, *n* (%)	9 (25)
Unicentric, *n* (%)	32 (88.9)
Oncological radicality***	
R0	36 (100%)
Residual disease (liver metastases)	7 (19.4)

* Ref. [14, 38]; ** Ref. [38]; *** Ref. [14, 38]

resections were chosen in such circumstances, that is, LCP and LDP [59, 60]. Currently, there are no randomized studies comparing enucleation with pancreatic parenchyma-sparing resections. In a recent meta-analysis, Hüttner et al. [61] reported a significant decrease in operative time ($p < 0.001$) and a similar length of hospital stay but a significantly greater incidence of pancreatic fistulas (OR 2.09, 95 % c.c. $p < 0.001$) for enucleations. However, postoperative endocrine insufficiency was found to be lower ($p < 0.001$).

In our series, conversion to open surgery was not necessary in any of the cases. This contrasts with the 9.5 and 6% conversion rates reported by other authors [54, 62]. In our series, the spleen was spared in all attempted cases ($n = 15$), with the splenic vessels also being spared. This, and the long operative times required to perform a middle pancreatectomy with enteric reconstruction, would also explain the mean operative time in our series—287 min. In this sense, this figure is very similar to that reported by other studies involving splenic vessels sparing [11, 63].

We opt to spare the splenic vessels whenever the spleen was preserved in contrast to what is done when the Warshaw technique is chosen. Whereas the benefits of sparing the spleen are widely accepted (a 1–5% reduction in post-splenectomy sepsis, a 50–70% decrease in mortality, a fall in splenoportal thrombosis and hematologic abnormalities), controversy surrounds sparing of the splenic vessels [64]. Given that there are no randomized prospective studies comparing both techniques, the most reliable scientific evidence comes from a systematic review of 401 patients undergoing laparoscopy in which in 256 patients (52%) splenic vessels were spared while 105 (30%) underwent the Warshaw procedure [65]. The degree of compliance success in the sparing of the vessels ranged from 55 to 84% in both open surgery and laparoscopy, which is indicative of the degree of technical difficulty [66–69]. The conversion

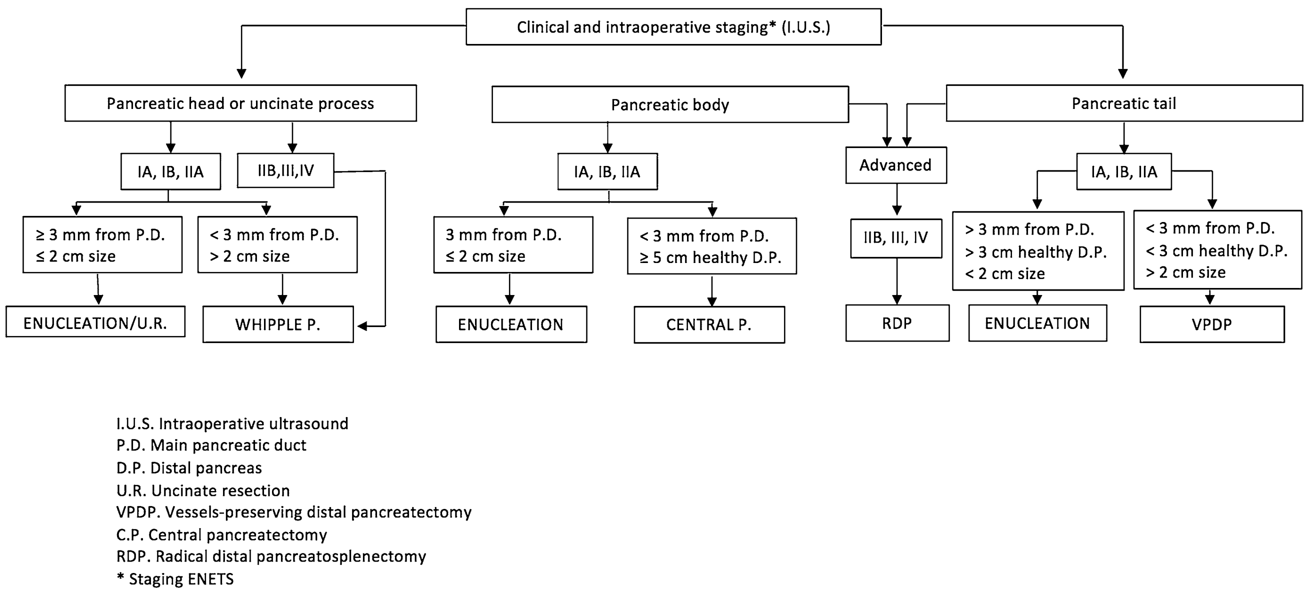

Fig. 1 The decision algorithm

rate to open surgery was 5.5%, and mean hospital stay was 7 days. There were no differences in the incidence of pancreatic fistulas [65, 66, 70, 71]. Of note, submucosal and perigastric varices developed in 4.2% of cases when the splenic vessels were not spared, and there was a significantly higher incidence of splenic infarction (22 vs. 1.9%; $p < 0.01$) (and chronic pain (38%), although only 2% of patients subsequently required splenectomy [65]). As above referred, in our experience, one patient treated with LVPDP required splenectomy after post-puncture abscesification of a peripancreatic fluid collection.

In the remaining 14 LVPDP cases, the splenoportal axis remained patent, with no abnormalities for 3–12 months after the operation. This is in contrast to Hwang who reported venous obliteration in 17.2% of cases [63]. This author has linked venous abnormalities to the handling and trauma of the vessels and the possible endothelial lesions caused by the ultrasonic dissector (Harmonic Scalpel, Ethicon Cincinnati, OH). As the splenic vein lacks a layer of muscle and elastic fibers, and has a lower pressure and less flow than the artery, it is more prone to endothelial thermal lesions caused by the blades of the ultrasonic dissector or other energy devices which can reach a temperature of 150 °C [72, 73]. As described in the technique section, we handled the vessels as little as possible and only used small titanium clips to seal the vessels supplying the distal pancreas. We did, however, assess the permeability of the vessels with an abdominal ultrasound, unlike Hwang and Yoon [63, 73] who used computed tomography to specifically study the permeability of the vessels 6 months after the operation.

We are aware that it is controversial to compare the incidence of pancreatic fistulas with data from groups who routinely leave drains in place given that the very definition of fistula requires the quantification of output and amylase, as defining ISGPF criteria [42]. Nevertheless, the results herein presented worth a comment, when a significant increase in such fistulas has been reported in resections for PNETs [62, 74–76]. Our results could be due to the low number of enucleations (1 case). It is well known that enucleations are associated with a higher incidence of pancreatic fistulas—around 36–50% in some series—than standard anatomic resections [74, 76], and this is why we prefer a LVPDP when the tumor is <3 cm from the tail and there is a scarce sacrifice of healthy parenchyma. Several reasons have been proposed for the high fistula rates in enucleations, including the softer texture of the pancreas in PNETs, the absence of a pancreaticojejunal anastomosis and inadvertent injury of the WD. A further reason for our results, which is consistent with reports from other authors, is the nonuse of any drainage in the pancreatic bed [77–79]. The routine use of drainage especially in limited resections of the pancreas has been associated with an increase in pancreatic fistulas [76, 77, 80]. In our series, we observed fluid collections in 13 patients, of which 11 were asymptomatic and resolved spontaneously. Presumably, if the drains had been left in place, some of these would have turned into grade A pancreatic fistulas [81]. We reserve drainage only for those patients showing any symptoms (pain, fever or compression of nearby structures, the same policy recommended by other authors [82, 83]). The two cases with symptomatic peripancreatic collections may be very well considered as grades B and C. Between some additional factors that may have also played a beneficial role could be the perioperative administration of octreotide which has been found to significantly reduce the number of fistulas in several prospective studies [84–87]. Finally, the importance of very careful technique without the use of the harmonic scalpel or other energy devices, avoiding small areas of necrosis as well as the intraoperative control of the integrity of the pancreatic duct, should not be underestimated.

In our series, four patients (11.1%) developed new-onset pancreatogenic diabetes mellitus (NODM) between 1 and 9 years after the operation. This figure is similar to that reported by other authors and the 14% reported in a recent meta-analysis [88–90]. In spite of the limited resection of the pancreas (<5 cm in maximum length in distal pancreatectomies) in our series, we observed endocrine insufficiency in 11% of cases. Bruijn et al. [88] and other authors have linked NODM with the resected volume of the pancreas [27, 91–93], and this in agreement with long-term experience reported in healthy donors undergoing hemi-pancreatectomy for pancreatic transplant. Twenty percent of such donors developed pancreatogenic diabetes [94]. It is well known that in humans, unlike in rodents, the proliferation of B cells is minimal following pancreatectomy [94, 95]. Other authors have linked the development of diabetes to complications such as pancreatic fistulas which affect the viability of endocrine tissue [89, 90].

Our study also has some limitations. It is based on a retrospective series from 2003 to 2015, a period during which a standard nomenclature was being established, and it was not until 2010 that firm histopathological criteria were laid down [5, 12, 14, 38, 46]. However, two of the authors exhaustively and separately reviewed the pathology reports, reaching a consensus when discrepancies in staging arose. Tumors were staged using both the ENETS and AJCC classifications, and a strong agreement was found between both. For this study, we decided to use the ENETS classification as it is more specific to PNETs [39, 46].

Similar arguments could be raised regarding the progress in surgical techniques and their complications. All the techniques were carried out by or under the supervision of the same surgeon and logically over the study period innovations which may have improved results were incorporated into a technique that requires great skill. We have already commented on the lack of prospective randomized studies comparing open and laparoscopic techniques, sparing of the splenic vessels or enucleation with standard resections, and thus, our multidisciplinary board followed consensus guidelines and the most reliable scientific evidence available at each moment.

Some strengths of this study deserve mention. Our evaluation is a single-center study of patients treated with homogeneous criteria that prevents lack of data conformity, a non-trivial and frequent limitation of multicenter studies.

Conclusion

The existing different surgical options must be individually considered according to the location and particular characteristics of every tumor. Results from this single-center study document the effectiveness of LOSP resections in selected cases of PNETs.

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Compliance with ethical standards

Disclosures Javier A. Cienfuegos, Joseba Salguero, Núñez-Córdoba Jorge M, Miguel Ruiz-Canela, Alberto Benito, Sira Ocaña, Gabriel Zozaya, Pablo Martí-Cruchaga, Fernando Pardo, José Luis Hernández-Lizoáin and Fernando Rotellar have no conflicts of interest or financial ties to disclose.

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