Reappraisal of Central Pancreatectomy  
A 12-Year Single-Center Experience

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Importance  Central pancreatectomy, as an alternative to standard resection for benign and low-grade pancreatic neoplasms, has been described in mainly small retrospective series.

Objective  To describe a large single-center experience with central pancreatectomy.

Design, Setting, and Participants  A retrospective case series in a tertiary referral center included 100 consecutive patients undergoing central pancreatectomy with pancreaticogastrostomy from January 1, 2000, to March 1, 2012.

Main Outcomes and Measures  Surgical indications, postoperative morbidity, mortality, and long-term outcomes regarding pancreatic function and recurrence.

Results  Central pancreatectomies were performed mainly for neuroendocrine tumors (35%), intraductal papillary mucinous neoplasms (33%), solid pseudopapillary neoplasms (12%), and mucinous cystadenomas (6%). The postoperative mortality rate was 3% (due to pulmonary embolisms in 2 patients and hemorrhage after pancreatic fistula in 1 patient). Clavien-Dindo III or IV complications occurred in 15% of patients and were due mainly to pancreatic fistula, requiring 10 radiologic drainage procedures, 7 endoscopic procedures, and 6 reoperations overall. After a median follow-up of 36 months, the rates of new-onset exocrine and endocrine insufficiency were 6% and 2%, respectively. Overall, 7 lesions could be considered undertreated, including 3 node-negative R0 microinvasive intraductal papillary mucinous neoplasms (without recurrence at 27, 29, and 34 months) and 4 node-positive neuroendocrine tumors (with 1 hepatic recurrence at 66 months). Among the 25 patients with a doubtful preoperative diagnosis, 9 could be considered overtreated (ie, operated on for benign nonevolutive asymptomatic lesions).

Conclusions and Relevance  Central pancreatectomy is associated with an excellent pancreatic function at the expense of a significant morbidity and a non-nil mortality rate, underestimated by the published literature. The procedure is best indicated for benign or low-grade lesions in young and fit patients who can sustain a significant postoperative morbidity and could benefit from the excellent long-term results.
The widespread use of cross-sectional imaging has led to increased diagnosis of low-grade pancreatic lesions, such as pancreatic neuroendocrine tumors (PNETs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystadenomas.1-3 If standard resections, including pancreateoduodenectomy or distal pancreatectomy, are widely accepted for malignant lesions, they might seem excessive for benign or low-grade malignant neoplasms. Indeed, if these procedures are now associated with low mortality rates in high-volume centers, their postoperative morbidity is still significant and their long-term results remain disappointing, especially in view of the high postoperative prevalence of pancreatic insufficiency.4

Parenchyma-sparing pancreatectomies, including enucleation and central pancreatectomy (CP), have been proposed as an alternative to standard resections for benign or low-grade lesions. If indications for enucleation are limited to small lesions, far from the main pancreatic duct,5,6 CP does not have these drawbacks; it can be performed for large lesions to the left of the gastroduodenal artery if the left pancreatic remnant is long enough.7,8 Initial results of CP have been enthusiastically received,9-12 as is often the case for emerging techniques, but few large and mature series have been published up to now.13-15

The aim of the current series was to describe a large single-center experience of CP with specific attention to surgical indications, postoperative morbidity, and long-term outcomes regarding recurrence and both exocrine and endocrine pancreatic function.

Methods

Data Collection
From January 1, 2000, to March 1, 2012, a total of 100 patients underwent CP in the Department of Hepatobiliary and Pancreatic Surgery, Beaujon Hospital, Clichy, France. Demographic variables, clinical presentation, preoperative workup, intraoperative data, postoperative course, and pathological findings were obtained from a prospective database with additional retrospective medical record review. Follow-up with clinical, radiologic, and laboratory assessments included outpatient routine postoperative visits with the surgeon. Tumors were classified according to the latest World Health Organization classification of exocrine and endocrine pancreatic neoplasms. Permission from the hospital’s institutional review board was obtained before data review and analysis; informed consent was not required.

Surgical Procedure and Indication
Preoperative tumor diagnosis and staging were performed using conventional imaging procedures, including computed tomography, magnetic resonance imaging, nuclear imaging, and/or endoscopic ultrasonography (EUS), at the surgeon’s discretion. All surgical indications were discussed by a multidisciplinary pancreatic tumor board, including surgeons, radiologists, pathologists, and gastroenterologists.

Central pancreatectomy was proposed for use in patients with symptomatic benign lesions, such as serous cystadenomas, as well as in those with low-grade neoplasms, including PNETs,8 branch and segmental main duct IPMNs, and mucinous cystadenomas. Lesions suspected before operation to be malignant (ie, PNETs associated with enlarged lymph nodes or distant metastasis, IPMNs, and mucinous cystadenomas with solid components or mural nodules larger than 5 mm in diameter) were not considered for CP,16 along with lesions presenting with worrisome symptoms suggestive of malignancy, such as weight loss, recent diabetes mellitus, continuous abdominal pain, and mass syndrome. Frozen-section biopsy on both sides was used selectively to intraoperatively exclude invasive cancer and more systematically to assess resection margins in IPMNs.17

The decision to perform CP was finally based on tumor location and decided during operation after surgical exploration assisted by intraoperative ultrasonography. If necessary, resection was extended to the right, with division of the gastroduodenal artery and pancreatic transection in the head along the bile duct. The proximal remnant was oversewn or stapled after elective ligation of the main pancreatic duct when possible.

Lymph node sampling was performed in patients with suspected PNETs or IPMNs. Reconstruction of the distal pancreas was performed by means of end-to-side pancreaticogastrostomy. If the distal pancreas was considered atrophic and smaller than 5 cm, only the left remnant was oversewn. Omentoplasty was performed and positioned between both pancreatic remnants and the splenic vessels. At the end of the procedure, 2 multichannel open silicone drains were usually placed close to the pancreatic section and pancreatic anastomosis and pulled through the right and left flanks.

Postoperative Course and Management
Biological assessment, including measurement of drain fluid amylase, was routinely performed on postoperative days 1, 3, 5, 7, and 10. Octreotide (Sandostatin; Novartis) was given postoperatively for 7 days (100 μg subcutaneously 3 times a day). Drains were progressively removed beginning on postoperative day 5 in the absence of postoperative pancreatic fistula (POPF). Patients with symptomatic POPF were treated with enteral or parenteral nutrition and drainage, as described elsewhere.18 Patients were usually discharged from the hospital only after complete resolution of POPF or all medical complications. Postoperative computed tomography was performed routinely in patients with POPF to exclude collection.

The postoperative mortality rate included all deaths occurring before hospital discharge or up to 90 days. Morbidity rates included all complications after surgery until discharge and/or readmission, classified according to the Clavien-Dindo classification.19 Amylase levels and postoperative courses were prospectively recorded, and POPFs and delayed gastric emptying were retrospectively graded according to the International Study Group of Pancreatic Surgery system.20,21 Clinically significant exocrine insufficiency was defined as symptoms (eg, steatorrhea and weight loss) resolving after pancreatic enzyme supplementation. Endocrine insufficiency was
defined as a fasting plasma glucose level of at least 7.0 mmol/L (to convert to milligrams per deciliter, multiply by 0.0555) and/or the need for diet modification, oral medication, or insulin use to control blood glucose levels.22

Final pathological results were retrospectively compared with suspected preoperative diagnoses. When an asymptomatic lesion without any potential risk for malignant transformation (ie, serous cystadenoma, pseudocyst, or simple cyst) was preoperatively misdiagnosed, we considered it overtreated. In contrast, invasive malignant lesions (ie, invasive IPMNs, node-positive PNETs, and adenocarcinomas), which in retrospect should have been treated with standard pancreatectomy and regional lymphadenectomy, were considered undertreated.

Statistical Analysis

Values are expressed as median (interquartile range [IQR]) or percentages, as appropriate. The Fisher exact test was used to compare differences in discrete or categorical variables, and the Wilcoxon rank sum test was used for continuous variables. All tests were 2 sided. For all tests, differences were considered statistically significant at \( P < .05 \). Data were analyzed with Stata 12 statistical software (Stata Statistical Software, Release 12; StataCorp).

Results

Patient and Tumor Characteristics

Patient characteristics are detailed in Table 1. Briefly, patients had a median age of 55.5 years (IQR, 41.5-64.5) and 67 of 100 were women. The most frequent circumstances of diagnosis were pancreatitis (32 [32%]), fortuitous discovery (31 [31%]) or nonspecific abdominal pain (22 [22%]). About half of lesions were cystic (47 [47%]), and their median diameter at radiologic imaging was 20 mm (IQR, 14-26 mm), without a significant difference between solid and cystic lesions (18 [13-25] mm; \( P = .44 \)). About 90% of patients underwent preoperative EUS, including EUS fine-needle aspiration biopsy in 37, revealing neuroendocrine tumor in 14, IPMN in 5, mucinous cystadenoma in 4, solid pseudopapillary neoplasm in 3, serous cystadenoma in 3, and renal cell carcinoma in 1, with noninformative findings in 7.

Intraoperative Results

Procedures and intraoperative results are detailed in Table 1. Central pancreatectomy was performed in 8% (n = 8) after enucleation failure because of main pancreatic duct injury. The median operative time was 245 minutes (IQR, 212-288 minutes), and the median intraoperative estimated blood loss was 250 mL (IQR, 100-300 mL). In 5% of cases (n = 5), CP was extended to the right based on frozen-section analysis of the pancreatic cut surface, with division of the gastro-duodenal artery and pancreatic transection in the head along the bile duct. In 2% of cases (n = 2), CP was extended to the left based on frozen-section analysis, resulting in a distal pancreatic remnant smaller than 5 cm and oversewn. The left pancreatic remnant was anastomosed to the posterior wall of the stomach in the other 98 patients. The splenic artery and vein were preserved in 99% of patients (n = 99).

Pancreatic consistency was soft on the right side in 75% of patients (46 of 61) and on the left side in 75% (45 of 61). About half of patients (52% (32 of 61)) had a soft pancreatic consistency on both sides, and only one-fourth (23% (14 of 61)) had a hard pancreatic consistency on both sides.

Postoperative Morbidity

Postoperative morbidity is summarized in Table 2. The mortality rate was 3% (n = 3). Two women, aged 68 and 73 years, died of pulmonary embolism on days 3 and 9 after CP for a mucinous cystadenoma and a nonfunctioning PNET, respectively. A 68-year-old man with severe coronary heart disease died of multiorgan failure on day 24 after CP for a main duct IPMN after major bleeding complicating a POPF.

The overall morbidity rate (including the 3% mortality rate) was 72% (n = 72), including severe complications (Clavien-Dindo classification III, IV, or V) in 18% of patients (n = 18). Post-
operative pancreatic fistula was the main cause of postoperative complications and occurred in 63% of patients, being clinically significant (ie, grade B or C) in 44%. The origin of the POPF could be determined in 57 of 63 patients, based on drain fluid amylase assessment and output and computed tomographic findings; POPF was presumed to originate from the pancreaticogastrostomy in 19% of patients (11 of 57) and from the right remnant pancreatic stump in 39% (22 of 57) and to be bilateral in 42% (24 of 57). In 6 of 63 patients (10%), the origin of the POPF remained undetermined. The median body mass index was higher in patients who developed POPF (24.1 vs 22.5 [calculated as weight in kilograms divided by height in meters squared]; \( P = .04 \)). No other predictive risk factors for POPF were identified (data not shown).

Excluding POPF, 26 other complications occurred in 21 patients, including surgical complications in 10 (delayed gastric emptying, small-bowel obstructions, wound abscess, and biliary fistulas after pancreatic transection along the common bile duct in 2 patients each and intra-abdominal fluid collection and pancreatitis in 1 patient each) and medical complications in 14 (infectious pulmonary complications in 4, urinary tract complications in 4, pulmonary embolisms in 3, central venous access complications in 2, and colitis in 1).

The reoperation rate was 6%, with most reoperations performed because of bleeding (n = 5) after POPF (n = 4) or early postoperative small-bowel obstruction (n = 1). Interventional procedures were needed in 10% of patients, including percutaneous drainage for septic collection (n = 7) and arterial embolization for bleeding (n = 3). Endoscopic pancreatic sphincterotomy was needed in 7% of patients (n = 7) to treat persistent POPF from the proximal pancreatic remnant.

The median length of stay was 25 days (IQR, 18-32 days). The readmission rate was 6%, with readmissions due to intra-abdominal fluid collections (n = 3), POPF (n = 1), pseudoaneurysm of gastroduodenal artery (n = 1), or small-bowel obstruction (n = 1).

**Pathological Analysis**

Pathological results are detailed in Table 3. The most frequent lesions were PNETs (35 [35%]), including 3 insulinomas and 1 gastrinoma; IPMNs (33 [33%]); solid pseudopapillary neoplasms (12 [12%]); mucinous cystadenomas (6 [6%]); and serous cystadenomas (3 [3%]). Pathological examination revealed 10 malignant lesions, including 4 PNETs with metastatic lymph nodes, 3 microinvasive IPMNs, and 3 pancreatic neoplasms.
renal cell carcinoma metastases. Lymph nodes were present in 76% of specimens, with a median of 3 harvested nodes (IQR, 1-6 nodes). Four patients (5%), all with PNET, had positive nodes.

Definitive diagnosis was similar to the suspected preoperative diagnosis in 90% of cases. Two of the 3 serous cystadenomas were misdiagnosed as branch duct IPMN, and the third was misdiagnosed as PNET. In 4 patients, a malignant lesion was preoperatively suspected but not confirmed by frozen-section biopsy and final pathological analysis. After final pathological analysis, 9 benign lesions could be considered overtreated: 3 simple cysts, 2 serous cystadenomas, 2 idiopathic main duct fibrotic stenoses, and 2 pseudocysts. In contrast, of the 10 malignant lesions, 3 were deliberately treated with CP (3 metastases from renal carcinoma), and 7 lesions were considered undertreated: 4 PNETs with positive lymph nodes and 3 IPMNs with microinvasive carcinoma. Two of these 7 lesions initially presented with symptoms (transient abdominal pain in 1 patient with a node-positive PNET and 1 with a microinvasive IPMN).

Long-term Results

Long-term postoperative results are shown in Table 4. After a median follow-up of 36 months (IQR, 12-54 months), 9% of patients (n = 9) experienced long-term complications, including 3 incisional hernias, 2 small-bowel obstructions, 2 persistent POPFs (beyond 90 days), 1 pseudocyst, and 1 superior mesenteric vein thrombosis. Regarding endocrine pancreatic function, new-onset diabetes (controlled by oral hypoglycemic medication) occurred in 2% of patients (n = 2), and preexisting diabetes worsened in 5% (n = 5). Regarding exocrine pancreatic function, 6% of patients (n = 6) required permanent pancreatic enzyme supplementation.

Overall, tumors recurred in 3% of patients (n = 3). Pancreatic tumors recurred at 58 and 59 months in 2 patients with renal cell carcinoma metastasis recurrence. Both patients underwent completion pancreatectomy and are still alive without further evidence of disease 34 and 29 months after reoperation. The third patient had a 30-mm Ro, grade 2, nonfunctioning PNET, with 2 positive lymph nodes. At 66 months, a single hepatic metastasis developed, which was treated with radiofrequency ablation; the patient was alive 14 months later, without evidence of disease. Median disease-free survival was not reached, and the rates of disease-free survival at 1, 2, 3, and 5 years were 100%, 100%, 100%, and 90% (95% CI, 67%-98%), respectively (Figure).

Discussion

Widespread use of cross-sectional imaging has led to an increased diagnosis of benign and low-grade pancreatic neoplasms,1-3 as well as identification of undetermined lesions, the management of which is often challenging. In this context, parenchyma-sparing resections, including CP, have recently been favored, even if results of CP in large and mature cohorts have been poorly documented. In this study, we found long-term pancreatic function after CP but at the expense of a significant morbidity rate and a non-nil mortality rate. This strongly suggests that CP is best indicated for benign or low-grade lesions in young and fit patients who can sustain serious postoperative complications and would benefit from the excellent long-term functional results.

Although there are now many articles reporting experience with CP, only 4 of them report an experience in more than 50 patients,13-15,23 with only 2 single-center series of 50 and 73 patients.13,14 Most early reports were enthusiastic, as is often the case for emerging and alternative techniques, possibly because of publication bias, with negative experience rarely being published (Table 5).

Our present report, to the contrary, is of a large mature experience from a single tertiary pancreatic surgery referral center, and it shows the complete picture of CP: surgical indications, postoperative mortality and morbidity rates, and long-term results, both functional and oncological. Our results contrast slightly with those in the published literature, underlining a significant overall morbidity rate, including an 18% rate of severe complications and a 3% mortality rate.

Although mortality rates after CP have not been highlighted in the past, a careful literature search does find similar rates.23-25 As could be expected from this technically challenging pancreatic procedure, postoperative deaths have occurred after both surgical23,25 and nonsurgical
complications, as in our experience. Furthermore, a reliable assessment of the postoperative mortality rate after CP should take into account all deaths occurring until at least postoperative day 90. Finally, there is probably some publication bias, with surgeons reluctant to report experiences with unfavorable results, leading to underreported mortality and morbidity rates. We believe, however, that the intrinsic risk of pancreatic surgery should not be underestimated for CP. It is noteworthy that the 3 postoperative deaths occurred in patients older than 65 years, suggesting that CP should be reserved for younger patients.

Whether the mortality rate for CP is higher than what can be expected after extended distal pancreatectomy is an important question. A recent systematic review comparing central and distal pancreatectomy did not show significant differences in mortality rates between the 2 procedures. Moreover, the postoperative mortality rate is not nil after distal pancreatectomy, and it increased to 3% at 90 days in a prospective randomized clinical trial reported in 2011.

The significant morbidity rate and length of stay after CP should also be highlighted. These are due mainly to a high rate of POPF, as reported by others. This can easily be explained by the presence of 2 pancreatic stumps. Reported POPF rates range from 7.7% to 63%, but on average most studies report a rate of about 30% to 40%. The discrepancy in reported rates is probably due to differences in definitions and assessment methods. In our experience, the systematic prospective drain fluid amylase assay could explain the high rate of pancreatic fistula at least in part. Overall, it seems logical that CP carries a higher overall risk of pancreatic fistula than other pancreatectomy procedures. It is performed mainly for benign lesions—that is, with a soft pancreas and a nondilated main pancreatic duct, which are consequently at higher risk of pancreatic fistula. The only POPF risk factor identified in our experience was a high body mass index, as reported elsewhere by others for pancreaticoduodenectomy or distal pancreatectomy.

It remains to be studied whether preventive measures such as octreotide administration, peripancreatic drainage, or modified pancreatic anastomosis could decrease this high rate of pancreatic fistula. Pancreaticogastrostomy was routinely used in the current series because it seems simpler during CP than pancreaticojejunostomy with a Roux-en-Y loop. It is unlikely that pancreaticojejunostomy could have decreased the POPF rate because both anastomotic techniques seem to provide equivalent results after pancreaticoduodenectomy. Nevertheless, a recent systematic review regarding CP revealed a higher but not statistically significant cumulative incidence of pancreatic fistula after pancreaticojejunostomy. Overall, these results emphasize that CP is not a risk-free procedure, and its benefit-risk balance must be taken into account.

Central pancreatectomy as the main alternative to extended left pancreatectomy is associated with a longer hospital stay, as reported by others, and a higher rate of postoperative morbidity, as reported in a recent systematic review of more than 650 patients, but also with a lower risk of pancreatic insufficiency. The up to 30% reported rates of de novo diabetes after standard pancreatic resections are no longer acceptable given the use of CP in asymptomatic young patients with long life expectancy or patients with symptomatic benign lesions. In this setting, parenchyma-sparing procedures have been developed to preserve long-term pancreatic function.
Our experience confirms the excellent long-term functional results after CP, with only a 2% rate of new-onset diabetes and a 6% rate of clinically significant exocrine insufficiency after a median follow-up of 3 years, far better than what is observed after standard resection. Results regarding exocrine function preservation after CP are not as convincing as those regarding endocrine function, as stated in a recent systematic review. Nevertheless, in the same review comparing CP with pancreatectomy for benign or low-grade lesions, the disease-free survival rate is excellent, up to 90% at 5 years in our series, in accordance with previously published findings. Consequently, patient selection is a key factor in ensuring the success of the procedure. Preoperative diagnosis is often doubtful, especially for cystic pancreatic lesions, which are preoperatively misdiagnosed in up to 25% of cases, even in experienced series.

In our series, preoperative diagnosis was also doubtful in 25% of cases and final pathological diagnosis not accurately predicted preoperatively in 10% of specimens. This exposes patients to the risk of either overtreatment (ie, resection of lesions that do not require surgery) or undertreatment (ie, performance of a suboptimal procedure for a malignant lesion). In our experience, 9% of resected lesions were asymptomatic and without any malignant potential (3 simple cysts, 2 serous cystadenomas, 2 main pancreatic duct fibrous stenosis, and 2 pseudocysts) and could therefore be considered as overtreated. This underlines the need for careful preoperative workup, including computed tomography and magnetic resonance imaging in addition to EUS with fine needle aspiration biopsy. These examinations need to be repeated if their initial quality is doubtful, which could help limit overtreatment. In these patients, performing CP instead of pancreaticoduodenectomy or distal pancreatectomy helps preserve pancreatic function.

Undertreatment may be more problematic because it might jeopardize long-term survival and because preoperative workup, including EUS with fine needle aspiration biopsy, often fails to identify node-positive small PNETs or microinvasive components of IPMNs. However, the risk of undertreatment could be limited by performing intraoperative frozen-section biopsy, early reoperation after final pathological diagnosis, or close postoperative follow-up, and it did not seem problematic in our experience. Avoiding undertreatment is of course easier with lesions such as IPMNs (with either branch duct or suspended main duct involvement), for which pathological findings are well correlated with outcome and intraoperative frozen-section biopsy findings are highly accurate. With PNETs, patient selection could be more challenging owing to the variable clinical evolution of these tumors. Nevertheless, the prognosis is excellent for a patient with a small, incidental, grade 1 lesion, even after a pancreas-sparing procedure. In this setting, peritumoral lymph node sampling should be advocated to better assess the biological behavior of these lesions. Overall, in our experience, CP seems an appropriate procedure, especially for lesions with a doubtful preoperative diagnosis.

Conclusions

Central pancreatectomy provides excellent long-term pancreatic function at the expense of a significant morbidity rate and a non-nil mortality rate, underestimated in the published literature. The benefit-risk balance of CP (a higher early morbidity rate counterbalanced by improved long-term pancreatic function) should be carefully compared with that of distal pancreatectomy (a lower early morbidity rate with a higher probability of long-term endocrine failure). Central pancreatectomy seems to be best indicated for benign or low-grade lesions in young and fit patients who are able to sustain serious postoperative complications and could benefit from the excellent long-term results.
Reappraisal of Central Pancreatectomy

Original Investigation Research