



Central pancreatectomy for benign or low-grade malignant pancreatic lesions - A single-center retrospective analysis of 116 cases



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ABSTRACT

Background: Central pancreatectomy (CP) is a parenchyma-sparing surgery for benign or low-grade malignant pancreatic tumors. This study aimed to evaluate the safety of the procedure and to analyze the long-term pancreatic function. The age-specific incidence ratio (IR) was calculated based on the incidence of diabetes mellitus in the general Italian population of Italy.

Materials and methods: Patients submitted to CP from January 1990 to December 2017 at the Department of General and Pancreatic Surgery of the Pancreas Institute of Verona, Italy, were evaluated.

Results: The final population was composed of 116 patients. There was a clear prevalence of females (74.1%), the mean age was 48 ± 15 years and the main indication for surgery was a pancreatic neuroendocrine tumor (45.7%). A pancreojejunal anastomosis was performed more frequently than a pancreogastric anastomosis (78.4% vs 11.6%). The mean length of stay was 20 ± 33 days.

The overall abdominal complications rate was 62%. The frequency of clinically relevant postoperative pancreatic fistula (grades B and C) was 26.7%. The mortality rate was 0%. The rate of R1-resection was 0.8%, as was the recurrence rate. After a mean follow-up of 12.8 years ± 6.5 , 6 patients developed new-onset diabetes (NODM, 7.5%), and the IR was 1.36 (95%CI 0.49–2.96).

Conclusions: CP is associated with high rates of abdominal complications, however, considering the amount of the normal pancreas that was spared, it might be indicated for selected benign or low-malignancy pancreatic tumors. CP patients have the same incidence of diabetes than the general population.

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Introduction

Parenchyma-sparing surgeries have been proposed for pancreatic surgery in order to better preserve the pancreatic function, when a resection of a benign or a low-grade malignant pancreatic tumor is needed. Central pancreatectomy (CP) and enucleation are the two most common types of parenchyma-sparing surgery. However, enucleation presents some limitations in case of big tumors (>3 cm) or even for smaller ones that are close to the main pancreatic duct. CP is an alternative treatment for tumors of the pancreatic isthmus or proximal body of the gland. For such tumors,

an extended distal pancreatectomy DP (with or without spleen-preservation) or an extended pancreaticoduodenectomy (PD) would be the only other radical treatments. In the long-term PD and DP are burdened by disappointing results in terms of deficit of exocrine and/or endocrine pancreatic function. Beger et al. found an incidence of new-onset diabetes mellitus (NODM) and exocrine pancreatic insufficiency after PD up to 22.2% and 49.1%, respectively [1]. In contrast, with respect to DP, De Brujin et al. reported a range incidences of NODM ranging from 14% to 39% [2]. Furthermore, the recovery of the endocrine and exocrine function after pancreatectomy happens in about a one-half of patients [3], having a clear impact on the quality of life and increasing the costs of pancreatic enzyme replacement therapy (PERT) and/or anti-diabetic drugs.

CP has been reported as a safe procedure, and patients are able to obtain a satisfactory preservation of the pancreatic function,

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even over the long-term [4]. Notably, the rates of morbidity, pancreatic fistula and reintervention are considerable [5]. Here, we report the largest single-center series of CPs published so far. In addition, in order to assess the endocrine function after surgery, we compared CP with an age-adjusted Italian population of subjects.

Methods

Data collection

The prospective electronically maintained database of the General and Pancreatic Surgery Unit of the Pancreas Institute of the University of Verona Hospital Trust (Verona, Italy) was queried for patients submitted to CP from January 1990 to December 2017. The Ethics Committee approved the study. Part of this series has already been analyzed and the results have been published by Crippa et al. in a multicenter setting [6]. Demographic data, comorbidities (categorized using the Charlson Age-Related Comorbidity Index – CACI [7]), intraoperative and postoperative data, and surgical pathology results were collected and reported. Paper medical records were investigated in case of missing data or discrepancies.

Surgical technique

CP was carried out as already classically described [8]. The reconstruction (end-to-side pancreojejunal [PJ] or pancreogastric [PG] anastomosis), the placement of a stenting within the main pancreatic duct, as well as, the number of drainages placed were done at each surgeon's discretion. Nodal sampling and lymphadenectomy were discretionary and rare, and the indications for this were not retrievable.

Postoperative complications

At 90-days after CP, the following postoperative complications were collected: postoperative pancreatic fistula (POPF), post-pancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE). All complications that were all graded and re-graded according to the new classifications internationally adopted [9–11]. The presence of abdominal collections and reintervention were reported too; whilst the severity of complication was reported using the Clavien-Dindo Classification [12].

Follow-up

The follow-up was made via telephone or out-patient consultations. Only patients with at least 12 months of follow-up were included. To assess the endocrine function patients were asked whether they had received a diagnosis of NODM (or worsening of their pre-existing diabetes mellitus), according to the general practitioner's prescription. As this study did not consider the possibility of performing or prescribing any medical tests we preferred to define "exocrine impairment" rather than "exocrine insufficiency" the presence of signs/symptoms of exocrine dysfunction (any presence of steatorrhea, flatulence, weight loss and/or other signs of unjustified malnutrition). Patients were submitted to a scrupulous checklist of questions that might reveal the presence of exocrine impairment [13]. The use or not of PERT was not considered per sé as a confirmation/disconfirmation of exocrine impairment. From an oncological standpoint, any possible recurrence of the disease was investigated. Patients lost to follow-up were considered as those uncontactable at the time of the analysis of long-term function.

Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc., IBM, Chicago, IL, USA). Categorical variables were reported as frequencies and continuous variables as medians with ranges or means with standard deviations, as appropriate. Statistical differences were detected using the χ^2 test, Student *t*-test, or Mann-Whitney test, as appropriate. *p* values < 0.05 were considered as statistically significant.

Age-specific incidences of diabetes were assessed through the age-specific incidence ratios (IRs), defined as the ratio of the observed to the expected number of patients developing diabetes. The 95% confidence interval (CI) of the IR was estimated using the Wilson and Hilferty approximation [14] of the exact Poisson distribution. The IR was considered significant when all values in the 95% CI did not contain unity.

To determine the expected number of cases of diabetes in the cohort, we used age-stratified data on the incidence of diabetes by the National Italian Institute of Statistics (ISTAT [15]).

Results

Demographic features, intraoperative data and final pathology

An overall number of 116 patients received CP at the authors' institution. Table 1 shows the characteristics of the study population. The mean age was 48 ± 15 years. There was a predominance of females ($n = 86$, 74.1%) and the mean tumor size was 24.1 ± 15.4 mm.

Ninety-one patients (78.4%) received a PJ anastomosis, whereas a PG anastomosis was performed in the remaining 25 cases (21.6%). Main pancreatic duct stenting was performed in 34 cases (28.8%). The stenting was not significantly associated with the development of overall abdominal complications or POPF. The mean operative time was 265 ± 62 min and the mean estimated blood loss was 293 ± 120 mL. Four patients (3.4%) were submitted to CP with a minimally invasive approach, and two of them (with a robotic-assisted approach) were converted to laparotomy due to technical reasons.

The final pathology revealed that the majority of tumors were pancreatic neuroendocrine tumors ($n = 53$, 45.7%), with a mean diameter of 24.7 mm (± 16.1). Forty-six (86.8%) were ≤ 20 mm, 6 (13.2%) were greater than 20 mm. The second and third most common diagnoses were serous cystadenomas ($n = 31$, 26.7%) and solid pseudopapillary tumors ($n = 17$, 14.7%). In 33 cases (28.4%) a lymphadenectomy/nodal sampling was performed, mostly for PanNENs (24/33, 72.7%). In four cases (3.4% overall, 12.1% of patients with lymphadenectomy/nodal sampling) metastatic lymph nodes were found, all of these were from pancreatic neuroendocrine tumors. Positive margins were found in one patient (0.8%) and two patients (1.6%) had a malignant disease in the specimen (two cases of invasive carcinoma-intraductal papillary mucinous neoplasm). However, neither subject was submitted to any further pancreatic resection.

Postoperative course

Abdominal complications occurred in 72 subjects (62%) and POPF was the most common one ($n = 64$, 62.1%). Considering only B and C POPF, 31 cases (26.7%) were registered. The second most frequent complication was the presence of abdominal collections ($n = 27$, 23.2%). When comparing PG anastomosis and PJ anastomosis, the first was statistically associated with higher rates of overall abdominal complications, (87.5% vs. 57.3%, $p = 0.005$), POPF (80% vs. 48.4%, $p = 0.004$), and abdominal collections (48% vs. 27.5%,

Table 1
Characteristics of the study population.

Feature	Value
<i>Demographic</i>	
Age, mean (y)	48 (±15)
Sex, female, n (%)	86 (74.1)
BMI, Kg/m ² , mean	26.4 ± 4.8
Preoperative diabetes, n (%)	4 (3.4%)
CACI > 4, n (%)	2 (1.7)
<i>Intraoperative</i>	
Operative time, mean (minutes)	265 ± 62
Estimated blood loss, mL	293 ± 120
Pancreojejunal anastomosis, n (%)	91 (78.4)
Mini-invasive approach, n (%)	4 (3.4)
Main pancreatic duct stenting, n (%)	34 (28.8)
<i>Final pathology</i>	
Tumor size, mean (mm)	24.1 ± 14.5
Specimen length, mean (mm)	38 ± 14
Diagnosis (n, %)	53 (45.7)
- Pancreatic neuroendocrine tumor [24]	47 (88.6)
G1	6 (11.4)
G2	7 (13.2)
Functioning (insulinoma)	31 (26.7)
- Serous cystadenoma	17 (14.7)
- Solid pseudopapillary tumor	7 (6)
- Intraductal papillary mucinous neoplasm (classified according to Adsay et al.) [25]	
LG	4 (57.1)
HG	1 (14.2)
iCa	2 (28.7)
- Mucinous cystadenoma	5 (4.3)
- Simple cyst	1 (0.9)
- Other	2 (1.7)
R1 resection	1 (0.8)
Lymph node analysis, patients, n (%)	33 (28.4)
Lymph node harvested, median (range)	1 (1–17)
Lymph node positive, patients, n (%)	4 (6.1)

BMI: body-mass index; CACI: Charlson Age-related Comorbidity Index; LG: low-grade; HG: high-grade; iCa: invasive carcinoma.

$p = 0.046$). The placement of a stent within the main pancreatic duct was not associated with nor prevented the development of any postoperative complications. Mortality was 0%. Table 2 shows the complications reported.

Functional and oncological follow-up

Table 3 reports data on functional and oncological follow-up. Two patients had a follow-up shorter than 12 months. Thus they

Table 2
Postoperative data.

Feature	Value
Length of stay, mean (d)	20 ± 33
Overall abdominal complications, n (%)	72 (62)
POPF, n (%)	64 (55)
CR-POPF, n (%)	31 (26.7)
Abdominal collection requiring therapy	27 (23.2)
PPH	9 (7.8)
-Grade A	2 (22.2)
-Grade B	4 (44.4)
-Grade C	3 (33.4)
DGE, n (%)	6 (5.1)
ICU admission, n (%)	9 (7.8)
Reoperation, n (%)	9 (7.8)
Readmission, n (%)	8 (6.8)
CDC ≥ 3, n (%)	42 (36%)
90-day mortality, n (%)	0

POPF: postoperative pancreatic fistula; CR-POPF: clinically relevant pancreatic fistula (grade B and grade C); DGE: delayed gastric emptying; ICU: intensive care unit; CDC: Clavien-Dindo Classification.

Table 3
Functional and oncological follow-up (n = 79).

Feature	Value
<i>Functional follow-up</i>	
NODM or worsening diabetes, n (%)	6 (7.5%)
Time from CP, mean (years)	15 ± 3.8
Exocrine impairment, n (%)	0
<i>Oncological follow-up</i>	
Recurrence rate	1 (0.8%)

NODM: new-onset diabetes mellitus; CP: central pancreatectomy.

were excluded from this analysis. Of the remaining 114, 79 (69.2%) patients were available for follow-up, while the rest were deceased or lost to follow-up for other reasons. The mean follow-up period was 12.8 ± 6.5 years. Six (7.5%) patients received a diagnosis of NODM, and those with a pre-existing diabetes did not experienced a worsening of that disease. The mean time since the development of NODM was 15 ± 3.8 years. When considering overall exocrine function, seven patients (8.8%) reported were reported to have to continued using PERT since surgery. Four other patients started PERT since surgery, but the therapy was suspended after 1, 2, 6, or 12 years. No other new cases of PERT were registered.

One patient diagnosed with an invasive carcinoma-intraductal papillary mucinous neoplasm experienced a recurrence of the disease at the head of the gland two years after surgery. He was submitted to a PD in another center, but he developed fatal post-operative complications. Another patient reported the recurrence of a serous cystadenoma at the head of the pancreas, which further treated with a PD.

Comparison of SIR of diabetes mellitus in CP patients

Considering only those subjects aged 48–71 years who developed NODM after a mean follow-up of 12 months (n = 6), and the national incidence of diabetes for that age range of 783/100000 cases/year, the IR was 1362 (95%CI 0,497–2965).

Discussion

The first two cases of CP with pancreoenteral anastomosis were described in 1957 in two patients with chronic pancreatitis [16]. In 1984, the technique was at first proposed for treating a neoplasm [8]. Since then, several series of CP have been proposed [4], the largest accounting for 100 patients [17]. The technique is considered safe in expert hands, yielding very good results in terms of sparing of the pancreatic function. Thus, CP is valid alternative to standard pancreatic resections for tumors of the neck or the proximal body of the gland [4,5]. Recently, a meta-analysis compared long-term results of CP alone and compared with DP and PD. The authors found statistically significantly lower rates of exocrine and endocrine pancreatic insufficiency [5]. CP is associated with higher rates of POPF, when compared with DP and PD. The reported rate of POPF from metanalytic approaches ranged from 30% to 40% [4,5] with spikes of 62% [5]. This findings are not novel as CP has two points of “weakness”, the proximal head stump and the distal one, which is anastomized to the jejunum or the stomach. Furthermore, the anastomosis is performed on a soft pancreas usually with a nondilated main pancreatic duct, because the indication for CP are is mostly for benign or low-grade malignant tumors.

Considering the demographic data, it is not surprising that the vast majority were females, that the mean age was young and that the tumor size was small. All this is explained by the indications for CP, namely benign or low-grade malignant pancreatic lesions in

young adults, where a parenchyma-sparing surgery is advisable. However, considering our caseload of pancreatic resection per year (>400), CP is performed very seldomly (3–4/year), since the patients are very selected. With regards to the surgical technique, we historically prefer to adopt the PJ anastomosis rather than the PG one. However, in the last 7 years, we report a greater prevalence of PG anastomosis over PJ anastomosis (data not shown).

Final pathology revealed that the majority of tumors were pancreatic neuroendocrine tumors (all cases were pancreatic neuroendocrine tumors). Notably, the clear majority of PanNENs was ≤ 20 mm, thus we may hypothesize that the strategy to proceed with a parenchyma-sparing surgery was done with the idea that the risk of nodal metastases would have been negligible. The analysis of the evolution of the surgical treatment of PanNET over time at our institution has been already published [18] and it is behind the aim of this study. In about a half of the cases a lymphadenectomy/nodal sampling was performed (24/53, 45.2%) and the mean tumor diameter of PanNENs with associated lymphadenectomy/nodal sampling was not significantly different than the one of PanNENs that did not received it (23.6 mm vs. 24.7 mm, $p = n.s.$). Thus, we might speculate that there was not at least a selection bias based on the diameter of the PanNEN. In four cases (6.1%) nodal metastases were found (three G1 and one G2 tumors). After a mean follow-up of 12.6 ± 6.2 years, none of these patients reported a recurrence of the disease. Nowadays, we can claim that in our experience CP was adequate for the treatment of PanNENs. Notably, our cohort of PanNENs was made mostly of small tumors and literature suggests that a conservative management might be a valid alternative to surgical treatment [19]. On the basis of this, we cannot exclude that the excellent oncological results we obtained are mitigated by the possibility that these tumors might have been managed safely with a conservative policy. Instead, CP should not be performed when the tumor is > 20 mm, due to the risk of nodal metastases.

Only one oncologically significant recurrence of the disease was reported, an invasive carcinoma-intraductal papillary mucinous neoplasm, which recurred at the head of the gland. Almost all resections were radical. In fact, only an R1-resection was reported for a non-functioning pancreatic neuroendocrine tumor, without nodal metastasis. The case was discussed multidisciplinary and, in accordance with the patient's wishes, it was decided not to proceed with further pancreatic resections and to shorten the follow-up interval.

The second most common diagnosis was serous cystadenoma. The majority of cases was operated on in the past 27/31 were operated on before 2010; for the remaining 4 operated afterwards the reasons for surgery were patient's wishes or preoperative misdiagnosis. Nowadays, the disease does not have an indication to surgery as it is a benign condition, unless it causes mass symptoms of obstruction. But in view of a possible surgical treatment, for serous cystadenomas increasing over time during follow-up located in the neck or proximal body tail of the gland, then a CP might be appropriate, as an obstructive chronic pancreatitis might have been developed upstream, reducing the risk of leakage of the pancreatic anastomosis.

With regards to postoperative course, our series report an overall high rate of POPF. However, stratifying POPF for the three subgrades and considering only the clinically-relevant ones (B and C), the rate drops down to an acceptable rate of 26.7%. This is in line with literature data and with the nature of the anastomosis that is usually performed on a soft pancreas with a nondilated main pancreatic duct. Interestingly, PG anastomosis was associated with higher rates of overall abdominal complications, POPF and abdominal collections. We found a high rate of PPH (7.8%). We do not have an explanation for this, because we did not find any

correlation between PPH and possible risk-factors [20] (such as POPF, abdominal collection, pancreas texture or type of anastomosis). Regardless, the small number of events ($n = 9$) was too small to perform a statistical analyses. Of note, two cases of PPH were treated endoscopically since a PG anastomosis had been performed and this anastomosis might be advantageous for this possibility over a PJ one. The stenting of the main pancreatic duct was not associated anyhow with the development of abdominal complications or POPF. Notably, we did not report mortality as other studies have [17,21]. In this sense, we confirm previous findings that the mortality associated with CP is nil or low [4,5], making CP more attractive than PD or DP, burdened by higher rates of postoperative deaths [22], even when they are performed for benign or low-grade malignant tumors [23]. The rate of minimally invasive approach was quite low, and it is not surprising considering the rarity CP.

The main objective of CP is to preserve the pancreatic function. A recent meta-analysis reported that pancreatic function is excellently preserved after CP, which is definitely better than after DP [5]. The present series shows a very low rate of NODM (7.5%) and a 0% incidence rate of exocrine impairment. Comparing our data with current literature on PD or DP, we strongly suggest performing CP whenever possible, keeping in mind that patients will probably experience complications, even serious ones. However, pancreatic function will be preserved over time. The IR value confirmed that the expected incidence of diabetes mellitus is equal to that of the general population.

In general, it must be highlighted that our population of CP patients is completely different than the one classically submitted to pancreatic surgery (sixty-year old subjects with periampullary malignancies, frequently already treated with medical oncological treatments). This is of utmost importance when making comparisons in terms of postoperative course and long-term pancreatic function. The functional reserve of a young adult patient and the underlying benign or low-malignant disease, typical features of a patient submitted to CP that represent a clear selection bias, should be always taken into account when comparing this surgery with PD and DP. At the time of preoperative consultation it should be highlighted that CP is associated with complications in more than a half of cases, but that the benefits in terms of pancreatic function preservation, will last for long.

The main limits of this study are linked to its retrospective nature, despite efforts were made to retrieve past medical records. Furthermore, the study period was long. Thus tens of surgeons succeeded with different stages of the learning curve and we did not retrieved data on CP cases that at the end were submitted to an extended DP or PD due to intraoperative complications or technical reasons. Finally, we changed our policy of transection and management of the cephalic stump within the years considered (e.g. hand-sewn closure of the pancreatic stump, ultrasonic transection, transection with mechanic stapler, application of sealants), and this might have impacted somehow on the postoperative course.

The strength of this study is its sample size, the largest published so far. We acknowledge that the majority of the cases of this series was previously published, however, we report the results of an almost doubled cohort, that became single-center, with the benefits connected (such as the homogeneity of the technique or the indications for it). We believe that these aspects give reliability to our findings. In addition, the satisfactory adherence rate to the follow-up provides consistence to our dataset on pancreatic function.

Conclusions

We acknowledge that our cohort encompass tumors for whom

nowadays CP or surgery itself might not be appropriate (such as small PanNENs, serous cystadenomas, small mucinous cystadenomas, solid pseudopapillary tumors). Anyway, on the basis of our short- and long-term outcomes we can claim that CP is a generally safe procedure that might be associated with serious complications. In our experience CP is not associated with mortality, it allows excellently the preservation of pancreatic function over time, and this is of paramount importance for pancreatic diseases with an excellent prognosis. In our analysis the age-adjusted incidence of diabetes mellitus in patients submitted to CP is not different from that of the general population.

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Informed consent statement

Not applicable to this study.

Conflict-of-interest statement

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