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Residual pancreatic function after pancreaticoduodenectomy is better preserved with pancreaticojejunostomy than pancreaticogastrostomy: A long-term analysis

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ABSTRACT

Background: Pancreatico-enteric anastomosis after pancreaticoduodenectomy can be performed using either a pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG). Differences in surgical outcomes are still a matter of debate, and less is known about long-term functional outcomes.
Methods: Twelve years after the conclusion of a comparative study evaluating the surgical outcomes of PJ and PG (Bassi et al., Ann Surg 2005), available patients underwent morphological and functional pancreatic assessment: pancreatic volume and duct diameter measured by MRI, impaired secretion after secretin, fecal fat, fecal elastase-1 (FE-1), serum vitamin D and endocrine function. Quality of life and symptom scores were evaluated with the EORTC QLQ-C30 questionnaire.
Results: Only 34 patients were available for assessment. No differences were found in terms of BMI variation, endocrine function, quality of life or symptoms. Exocrine function was more severely impaired after PG than after PJ (fecal fats 26.6 ± 4.1 vs 18.2 ± 3.6 g/day; FE-1 121.4 ± 6.7 vs 170.2 ± 25.5 μg/g, vitamin D 18.1 ± 1.8 vs. 23.2 ± 3.1 ng/mL). MRI assessment identified a lower pancreatic volume (26 ± 3.1 vs. 36 ± 4.1 cm^3) and a more dilated pancreatic duct (4.6 ± 0.92 vs. 2.4 ± 0.18 mm) in patients with PG compared to those with PJ.
Conclusion: Compared to PJ, PG is associated with a more severely impaired exocrine function long-term, but they result similar endocrine function and quality of life. In patients with a long life expectancy, this should be taken into account.

Introduction

The pancreaticoduodenectomy is one of the most challenging surgical procedures complicated by major short-term complications and mortality [1]. The pancreatico-enteric anastomosis represents the most challenging aspect of this procedure, as a postoperative pancreatic fistula (POPF) is the most important complication, occurring in 5–26% of cases [2–5]. A POPF is responsible for the appearance of other associated major complications, such as delayed gastric emptying (DGE), post pancreatectomy hemorrhage (PPH), length of hospital stay (LHS) and high costs of patients' management [6].

Pancreaticojejunostomy (PJ) is the most frequently performed anastomosis worldwide [2], whereas pancreaticogastrostomy (PG) has gained popularity through the years as a result of a possible reduction in POPF incidence. Several randomized controlled trials and metanalyses [7–10] have been published reporting variable results which at least partially converge towards the evidence that the PG method is able to reduce and mitigate the likelihood of a POPF.

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The lack of any substantial short-term difference implies that the use of a particular anastomosis is left to the surgeon's discretion. However, attention should be paid to the potential long-term consequences in patients with long life expectancies. Both techniques can potentially produce severe exocrine pancreatic insufficiency due to a reduced residual pancreatic volume and impairment of pancreatic stimulation, which, in physiologic conditions, is induced by endocrine cells of the resected duodenum. A PG has the potential to produce even more severe disruption of digestion since it diverts the secretion of both pancreatic enzymes and bicarbonates into the stomach. Here, pancreatic enzymes may be destroyed, particularly when the luminal pH falls below 3 [11] or when gastric emptying is delayed, as often occurs after PD [12]. The actual clinical relevance of these considerations has not been completely identified. Studies with a short follow-up [13,14] have been unable to detect differences between PG and PJ in terms of functional long-term outcomes assessing only qualitative or subjective parameters (performance status, weight, bowel movements).

The aim of the present study was to provide a comprehensive comparison between PG and PJ in terms of long-term functional outcomes measured by exocrine and endocrine function and digestive capacity.

Materials and methods

The study population was composed of patients already enrolled in a prospective comparative study evaluating surgical outcomes of PG compared to PJ published by the promoting Institution [15]. All patients included in the comparative study presented a soft pancreatic stump with a non-dilated (<5 mm) main pancreatic duct. All the surgical procedures were performed in the Department of General and Pancreatic Surgery – The Pancreas Institute from 2001 to 2005. The present study was approved by the Institutional Review Board (approval number for all retrospective studies 1101 CESC, informed consent waived) and follows the recommendations of STrengthening the Reporting of OBservational studies in Epidemiology *(STROBE)*. Both PJ and PG were completely standardized at our Institution. PG was carried out on the posterior wall of the stomach by a single layer of nonabsorbable interrupted stitches after a generous mobilization of the gland to pushing it directly into the gastric cavity. PJ was carried out using a single-layer technique ("dunking" PJ) or adding another layer between the main pancreatic duct and the jejunal loop ("duct-to-mucosa" PJ).

Patients who had disease recurrence, were undergoing adjuvant radiotherapy, were older than 75 years old or were affected by chronic pancreatitis, chronic renal failure, chronic heart failure, liver cirrhosis or gastrointestinal disorders were excluded to avoid potential sources of bias potentially affecting pancreatic function and quality of life.

Beginning in 2011, patients with at least 10 years of follow-up after surgery were contacted to propose participation in the present study. Those who accepted were scheduled for hospitalization to carry out a fecal balance study, an MRI and a series of functional pancreatic studies. Patients were instructed to start a diet consisting of 100 g of fat and to stop proton pump inhibitors and pancreatic enzymes two days before admission to the hospital. The MRIs were scheduled after the end of fecal collection to avoid interference with the diet.

Serological tests

The following biochemical tests were performed: pancreatic amylase, lipase, serum albumin, prealbumin, vitamin D and vitamin B12. The presence of endocrine insufficiency was evaluated by measuring fasting venous glucose, with postprandial glycemic sticks and by glycated hemoglobin levels. Patients with overt diabetes at the time of surgery were excluded from this latter comparison.

Fecal studies

Fecal studies were carried out on homogenized stools collected during the last three days during the 100 g of fat diet. Fecal fat was measured with a titrimetric variant of the van De Kamer method [16]. Fecal elastase-1 (FE-1) concentration was measured with an ELISA monoclonal assay (ScheBo, Meridian Bioscience Europe, Milan, Italy) and expressed as μg/g of wet stools. Pancreatic function was classified according to FE-1 levels as normal (>200 μg/g), mildly impaired (100–200 μg/g) or severely impaired (<100 μg/g) [17].

Magnetic resonance imaging

A piece of 1,5 T equipment was used (Magnetom Symphony; Siemens, Erlangen, Germania). MRI was used to quantify pancreatic secretion, residual volume and main pancreatic duct diameter. Pancreatic volume was measured by T1-dependent Volumetric Interpolated Breath-hold Examination (VIBE) (parameters: TR = 3,5 ms, TE = 1,6 ms, with a 512 × 512 pixel matrix and a fixed, 3.4 mm thickness) in the venous phase after paramagnetic contrast medium infusion. From these sequences, a manual selection of the pancreatic region of interest (ROI) was obtained, and its surface was calculated. A single volumetric ROI, representing the pancreatic volume in mL, was then obtained by a volumetric interpolation algorithm of all the ROIs. A series of 34 patients with chronic asymptomatic hyperenzymemia was used to check for intra and inter-observer reproducibility of pancreatic volumes by two radiologists. The results showed a good intra and inter-observer reproducibility with linear coefficients "r" of 0.88 and 0.82, respectively. The residual pancreatic volume was calculated for the present study as the mean of the measurements by the two radiologists. In the absence of a series of MRIs performed on healthy patients, the mean normal pancreatic volume was obtained from 67 patients with chronic asymptomatic hyperenzymemia without clinical or morphological signs of pancreatic diseases [18] and equaled 107.3 ± 4.3 mL.

The cholangiopancreatography study was performed at baseline and repeated after the infusion of secretin (Secrelux, 1 CU/kg) every 30 s for 5 min and then every minute for 5 min according to our institutional protocol [19]. Duct diameter was measured at the point with maximal dilatation within 2 cm of the anastomosis. The threshold to define a nondilated pancreatic duct in the body/tail of the pancreas was 3 mm.

The analysis of pancreatic secretion is usually based on duodenal landmarks that are lost after pancreaticoduodenectomy. Secretin stimulates biliary secretion and inhibits gastric secretion, and for this reason, any pancreatic secretion is overestimated in cases of PJ due to the increased secretion of bile, whereas it is not in cases of PG. For the present study, only a qualitative evaluation of secretion (normal or impaired) based on the judgment of a radiologist with extensive experience in MRI analysis of the pancreas (RM) was provided.

Quality of life

Quality of life was measured with the EORTC QLQ-C30 [20,21]. The questionnaire contains a global health status/quality of life scale, five functioning scales (physical, role, emotional, cognitive

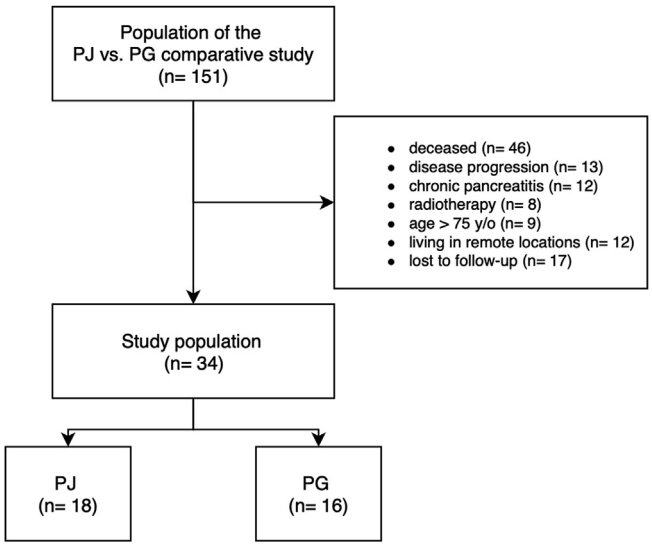

Fig. 1. STROBE compliant study flow-chart.

and social functioning), three symptom scales and six single items. Normal values for healthy subjects were not available for an Italian population and were therefore taken from a large cohort of Germans [21].

Statistical analysis

Data analysis was carried out using SPSS statistical analysis software (version 21, IBM Italia, Milan). The distribution of the variables is reported as the mean with standard deviation. The normal distribution of the parameters was investigated by using the Kolmogorov-Smirnoff test; when necessary, a logarithmic transformation was used to normalize the distribution of results. Student's t-test for independent data was used for normally distributed variables, and the Kolmogorov-Smirnov test was used for non-normally distributed and not continuous variables. Fisher's exact test was employed to compare two proportions. We considered a p-value of 0.05 as the limit for statistical significance.

Results

Of the 151 patients included in the previously published comparative study [15], 17 were lost during follow-up. Of the remaining 134 patients, only 34 participated in the present study. The final study population was composed of 16 (47%) patients who underwent PD with PG and 18 (53%) with PJ. Fig. 1 shows the STROBE compliant flowchart.

Table 1 shows patients' characteristics. There were not statistically significant differences between the PJ and PG group except that a greater number of pancreatic supplements were prescribed on the basis of the clinical assessment of patients undergoing PD with PG.

Serological tests

Table 2 shows the results of biochemical tests in the two groups. Albumin, cholesterol, triglycerides and vitamin B12 were normal and not significantly different between the two groups. Four patients (3 in the PG and 1 in the PJ group) were receiving intramuscular vitamin D supplements and were excluded from the analysis of serum levels of vitamin D. Vitamin D was severely reduced in both groups but was significantly more reduced in the PG group compared to the PJ group. In the PG group, only two patients presented with a moderate vitamin D deficiency (between 20 and 30 ng/mL); in the remaining patients, there was a severe deficiency (<20 ng/mL). Among the PJ patients, 50% had a mild and 50% had a severe vitamin D deficiency. A significant moderate correlation was found in the whole series between vitamin D levels and fecal fat excretion measured in the absence of oral lipase supplementation ($r^2 = 0.34$, $p = 0.02$).

Fig. 1A shows serum levels of pancreatic amylase and of immunoreactive lipase in patients with PG (closed bullets) or PJ (open bullets) anastomoses. Values below the lower normal limit are significantly more frequent in PG than in PJ (pathologic amylase values: 94% vs 44%, respectively, $p = 0.003$; pathologic lipase values: 81% vs 39%, respectively, $p = 0.017$). Mean values of these serum pancreatic enzymes were severely affected by one outlier, a patient presenting with severe stenosis of the PG, marked dilatation of the pancreatic duct and clear signs of obstructive pancreatitis with severe pancreatic atrophy who chronically presented with abnormally high values of pancreatic amylase and lipase (64

Table 2
Biochemical tests of patients comparing the long-term results after PD with PG compared to PD with PJ.

	PG (n = 16)	PJ (n = 18)	P
Vitamin D (ng/mL)	14.3 ± 2.0	22.2 ± 3.2	0.01
Vitamin B12 (pg/mL)	497 ± 62.7	416 ± 52.4	NS
Albumin (g/L)	42.3 ± 0.9	43.3 ± 0.7	NS
Pre-Albumin (g/L)	0.2 ± 0.1	0.2 ± 0.01	NS
HbA1C (%)	6.3 ± 0.2	6.2 ± 0.2	NS
Cholesterol (mg/dl)	165.4 ± 9.9	161 ± 8.0	NS
Triglycerides (mg/dl)	89.7 ± 11.1	84.1 ± 5.5	NS

Table 1
Patients' characteristics.

		PG (n = 16)	PJ (n = 18)	P
Pathology	Intraductal papillary mucinous neoplasm	2	7	NS
	Ampullary cancer	5	3	
	Neuroendocrine neoplasia	3	4	
	Pancreatic ductal adenocarcinoma	2	1	
	Serous cystadenoma	2	1	
	Mucinous cystadenoma	1	0	
	Solid pseudopapillary tumor	1	0	
	Inflammatory pseudotumor	0	2	
Male/female ratio		6/10	12/6	NS
Age (years, mean, SD)		58.1 ± 2.6	58.4 ± 2.6	NS
BMI at surgery (Kg/m^2, mean, SD)		22.8 ± 0.8	25.3 ± 1.0	NS
BMI at present hospital admission		22.4 ± 0.6	24.9 ± 0.8	NS
Oral lipase supplements (IU/day)		65000 ± 11200	33000 ± 7700	0.02

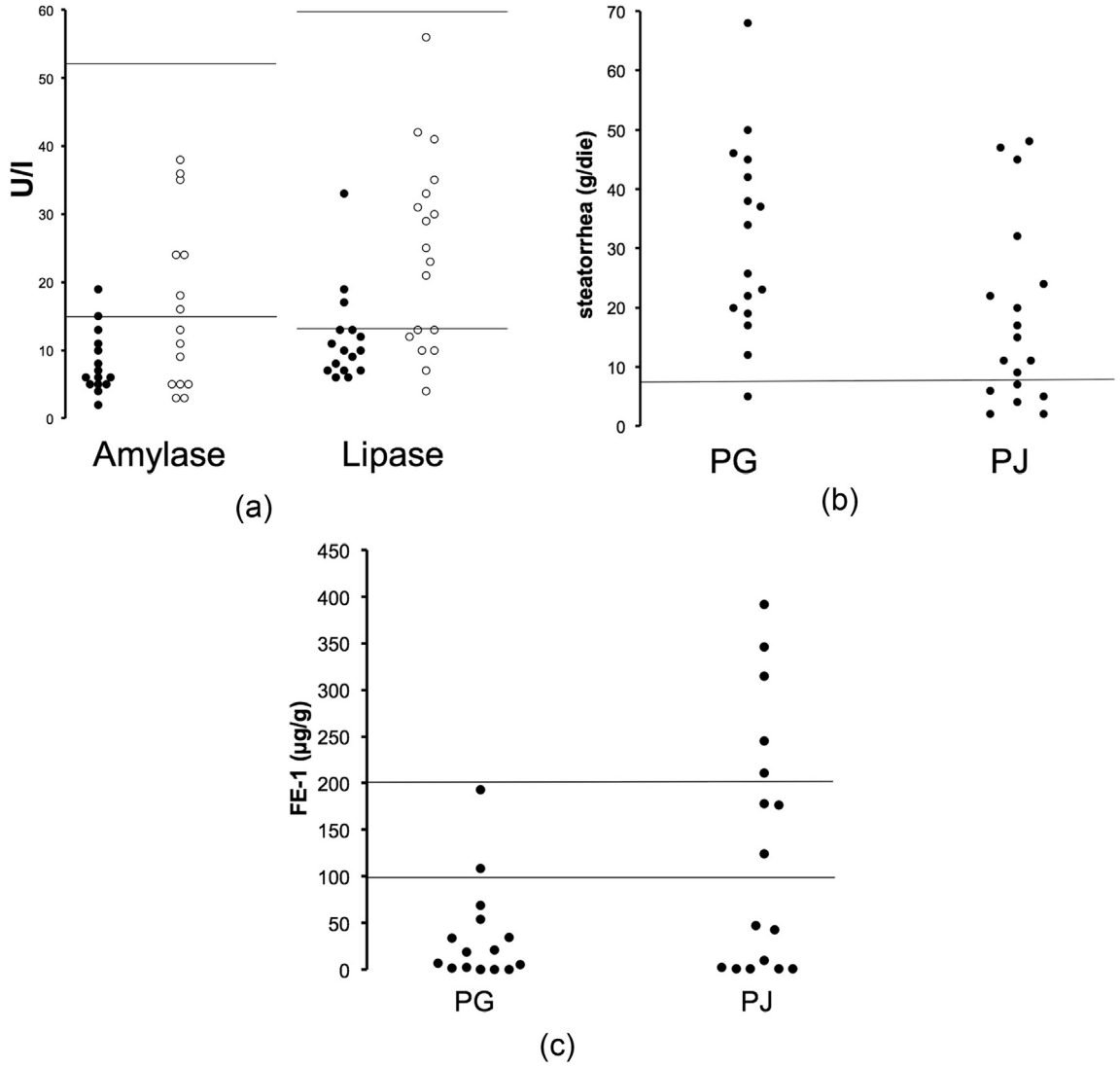

Fig. 2. A) Amylase and lipase values in the serum comparing patients with PG (closed bullets) and PJ (open bullets). Horizontal lines: limits of the normal range. B) Fecal fat values in the two groups of patients. Horizontal line: upper limit of normal value. Steathorrea is more common in PG than in PJ patients ($p = 0.02$). C) FE-1 values. Values > 200 µg/g are normal, values < 100 µg/g are suggestive of severe pancreatic exocrine insufficiency. All patients presented with an abnormal value, but in PG patients, FE-1 was more severely impaired, and the difference in PJ patients was statistically significant ($p = 0.001$).

and 128 U/L, respectively). After excluding this outlier, mean values of both enzymes were significantly lower in the PG group than the PJ group (amylase: 7.8 ± 1.2 vs 18.8 ± 3.1 U/L; $p = 0.003$; lipase 11.9 ± 1.8 vs 24.2 ± 3.3 U/L; $p = 0.003$).

In both groups, there was a tendency to develop glucose intolerance/diabetes, but the difference in HbA1c level between the PG and PJ groups was not significant (6.3 ± 0.2 vs $6.2 \pm 0.2\%$, $p = NS$).

Fecal tests

Given a normal value of <7 g/day, all patients had high levels of fecal fat (24.4 ± 2.9 g/day). A clinically relevant steatorrhea was found in 93.75% of PG and 66.6% of PJ patients ($p = 0.09$), and patients with PG had significantly higher levels of fecal fat (Fig. 2B, 31.5 ± 4.1 vs 18.2 ± 3.6 g/day; $p = 0.02$).

A severe reduction in residual exocrine function, as highlighted by FE-1 values of wet stools <100 µg/g, was found in 87.5% of PG and 44.5% of PJ patients ($p = 0.013$). Patients with PG had significantly lower levels of FE-1 when compared to patients with PJ after logarithmic transformation of the variable to normalize the distribution (Figs. 2C and 38.4 ± 25.8 µg/g vs 121.4 ± 27.5, $p = 0.002$).

MRI findings

Pancreatic volume was markedly reduced after surgery in comparison to the control population of 67 patients with chronic asymptomatic hyperenzymemia. Residual volume in patients who underwent an operation was 31.6 ± 2.73 mL, with a mean reduction of 70% compared to nonoperated controls (107.3 ± 4.3 mL). The residual pancreatic volume was inversely correlated with steatorrhea (Fig. 3A). Residual volume was significantly lower after PG than after PJ (Figs. 3B and 26 ± 3.1 vs 36 ± 4.1 mL, $p = 0.05$).

Fig. 3C shows the maximum diameter of the main pancreatic duct within 2 cm of the anastomosis. Values are not normally distributed, mainly due to a skewed distribution in the PG patients. As already reported, in one patient, the diameter of the pancreatic duct was markedly increased (17 mm) in the absence of abdominal pain. After logarithmic transformation, the mean diameter was

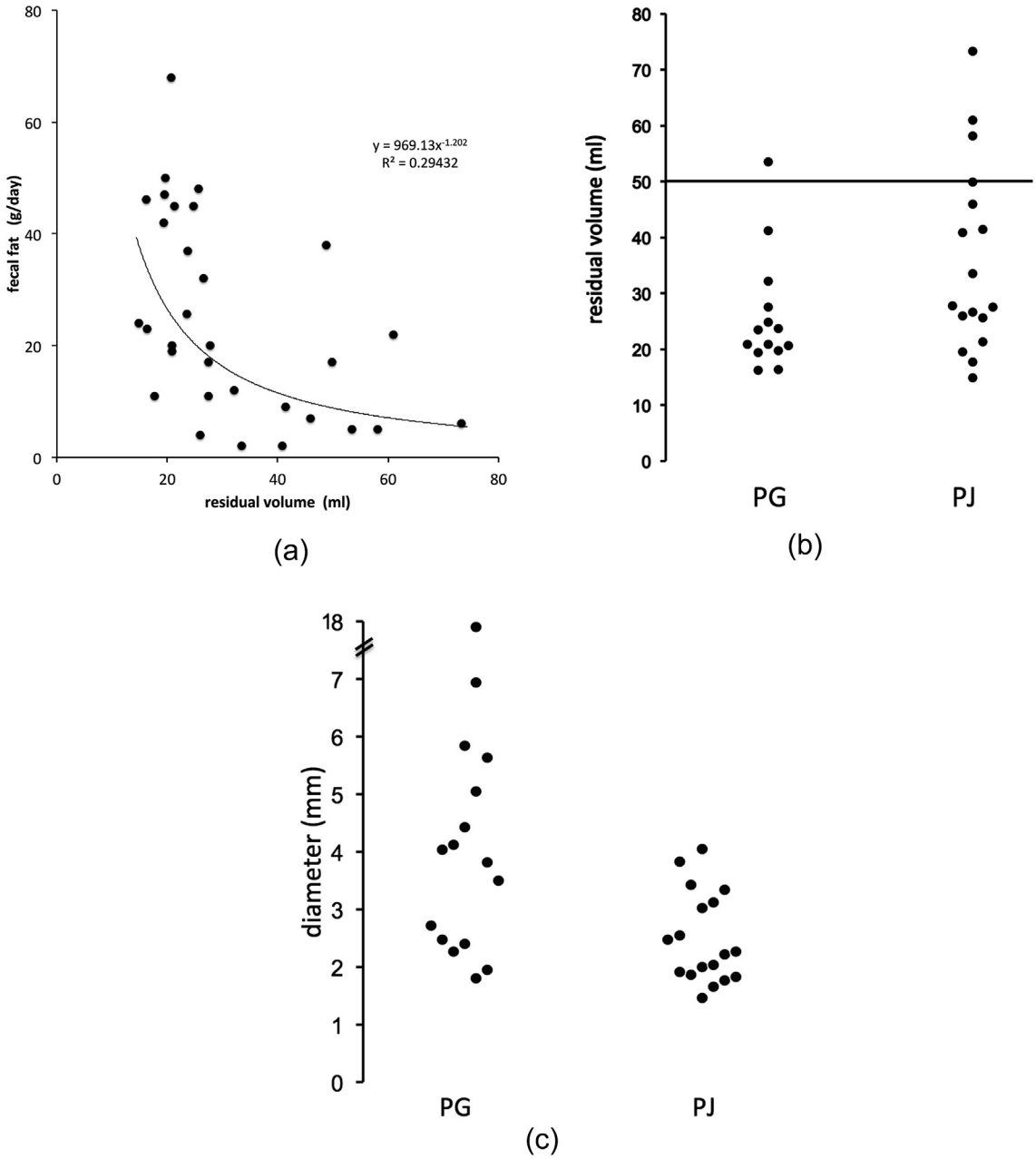

Fig. 3. A) Relationship between fecal fat and residual pancreatic volume (as measured by MRI) in the studied patients. Line: best fit correlation line, as calculated by a power equation. B) Residual pancreatic volume in PG and PJ patients. Horizontal line: lower limit of normal, as calculated from patients with chronic pancreatic hyperenzymemia. C) Maximal diameter of the main pancreatic duct within two cm of the anastomosis.

clearly increased after PG anastomosis (4.6 ± 0.92 vs 2.4 ± 0.18 mm; $p = 0.04$). This result was not affected by the exclusion of the outlier. A severe impairment in the volume of pancreatic secretion after secretin infusion was considered to be present in 50% of PG and in 28% of PJ patients, but the difference was not significant ($p = 0.291$).

Quality of life

Fig. 4 shows quality of life (A) and symptomatic scales (B). No differences were found between patients with PG or PJ. Additionally, no differences were found when comparing patients who underwent PD to the control population extracted from a large series of outpatient clinic patients [21]. In 6 out of 8 symptomatic scores, the median value was 0, suggesting an almost complete absence of symptoms in patients who underwent PD.

Discussion

The comparison between PG and PJ has always focused on short-term results, as POPF development represents the major complication of pancreatic surgery. Previous reports failed to show a predominance of one anastomotic technique over the other, so both anastomoses have become part of the technical knowledge of a skilled surgeon who then chooses to perform the anastomosis with which he feels more confident.

Potential differences in long-term functional outcomes between PG and PJ represent a major issue, and they have not yet been

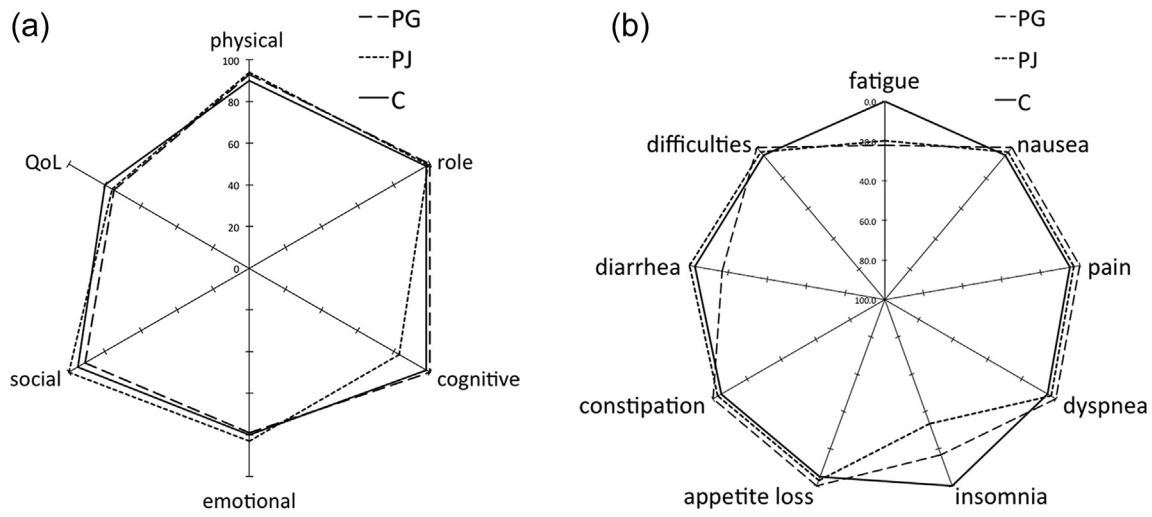

Fig. 4. A): Radar graph of the parameters used to quantify the quality of life. Mean values are reported on a scale of 0–100. Controls (continuous line) are patients coming from a large series of outpatient clinic subjects. Broken line: PG; dotted line: PJ. B) Radar graph of the symptom scores. Higher values mean that patients presented with severe symptoms.

clearly defined. These differences could lead to selecting one technique rather than the other in patients with a long life expectancy.

The present study has the longest available follow-up (at least 10 years) and compares functional outcomes of these two anastomoses. It demonstrates that PG is associated with a more severe derangement of exocrine pancreatic function. This result is in line with previously published reports [22].

First, serum levels of vitamin D were reduced in most patients, but they were more severely reduced after PG. Serum values reflect the amount of vitamin ingested and absorbed in patients on a free diet and during the prescribed enzyme supplementation period. Low vitamin D levels indicate that the need for pancreatic enzyme supplementation is not met by the dose prescribed by general practitioners or by board certified surgeons or gastroenterologists. This indirect evidence that enzyme replacement is often inadequate is in line with previously published studies [23,24].

In the present series, the presence of exocrine pancreatic insufficiency is confirmed by the reduced levels of pancreatic enzymes both in serum and in stool. FE-1 is related to fecal fat by a power correlation line. In the present series, steatorrhea was found even in patients with moderate reductions in FE-1.

FE-1 could have only a limited diagnostic value in patients undergoing PD. On one hand, the FE-1 value is normal only in 20% of patients undergoing PD due to the reduced volume of residual functional parenchyma. On the other hand, steatorrhea may be present even in patients with normal or only moderately reduced FE-1 for a number of reasons (reduced pancreatic volume, reduced secretion due to the absence of hormonal stimulation by the duodenum, irregular mixing with bile). In any case, fat malabsorption is more severe after PG. There are many possible explanations for this result. First, after PG, pancreatic enzymes are secreted within the stomach, and acid secretions could potentially cause an irreversible inactivation of enzymes, such as lipase. This may be relevant in the long-term after the onset of chronic damage to the residual pancreatic stump, which reduces the secretion of bicarbonate within the stomach and therefore produces a greater acidification of gastric content. Moreover, acid secretion activates trypsin which progressively leads to the digestion of the pancreatic parenchyma.

In line with these considerations, the residual pancreatic volume is markedly reduced after PD. Unfortunately, data about pancreas volumes before surgery were not available; however, qualitatively we detected a progressive postoperative atrophy of the residual pancreas.

No differences were found when comparing PG and PJ in terms of quality of life or symptoms. Other studies about quality of life after PD [25] showed a worsening quality of life only in the first months following surgery with subsequent recovery to preoperative levels. This response suggests that in the early postoperative period, other factors may influence the quality of life in patients. High scores for quality of life and low scores for the reporting of symptoms may also indicate that the EORTC QLQ-C30, the questionnaire suggested for patients with malignant disease, could not be the most suitable for the present study where the study population is mostly composed of patients with low-grade malignant or borderline malignant disease. The present study has several limitations. To obtain a long-term follow-up, many years have passed since the end of the previous prospective comparative study evaluating surgical outcome of PG vs. PJ. Many patients died due to primary disease and others were lost to follow-up. This must be taken into account as it could produce a potential selection bias as well as a reduced sample size.

Conclusion

Even if performing a PG is a straightforward technique for pancreatic anastomosis, in the long-term, it is associated with a more severe impairment on exocrine function, greater reduction in pancreatic volume and dilatation of the pancreatic duct. Although these differences may not be as marked in the first years after surgery, they represent a major issue that should be taken into account when performing PD in patients with a long life expectancy.

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R. Cardobi, C. Sozzi: MRI analysis.

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