J Gastrointest Surg (2012) 16:1686–1695
DOI 10.1007/s11605-012-1940-4

ORIGINAL ARTICLE

Randomized Controlled Single-Center Trial Comparing Pancreatogastrostomy Versus Pancreaticojejunostomy After Partial Pancreatoduodenectomy

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Received: 30 March 2012 / Accepted: 15 June 2012 / Published online: 29 June 2012

Abstract
Background The aim of this single-center randomized trial was to compare the perioperative outcome of pancreatoduodenectomy with pancreatogastrostomy (PG) vs pancreaticojejunostomy (PJ).
Methods Randomization was done intraoperatively. PG was performed via anterior and posterior gastrotomy with pursestring and inverting seromuscular suture; control intervention was PJ with duct–mucosa anastomosis. The primary endpoint was postoperative pancreatic fistula (POPF).
Results From 2006 to 2011, $n=268$ patients were screened and $n=116$ were randomized to $n=59$ PG and $n=57$ PJ. There was no statistically significant difference regarding the primary endpoint (PG vs PJ, 10 % vs 12 %, $p=0.775$). The subgroup of high-risk patients with a soft pancreas had a non-significantly lower pancreatic fistula rate with PG (PG vs PJ, 14 vs 24 %, $p=0.352$). Analysis of secondary endpoints demonstrated a shorter operation time (404 vs 443 min, $p=0.005$) and reduced hospital stay for PG (15 vs 17 days, $p=0.155$). Delayed gastric emptying (DGE; PG vs PJ, 27 vs 17 %, $p=0.246$) and intraluminal bleeding (PG vs PJ, 7 vs 2 %, $p=0.364$) were more frequent with PG. Mortality was low in both groups (<2 %).
Conclusions Our randomized controlled trial shows no difference between PG and PJ as reconstruction techniques after partial pancreatoduodenectomy. POPF rate, DGE, and bleeding were not statistically different. Operation time was significantly shorter in the PG group.

Keywords Pancreatoduodenectomy · Pancreatogastrostomy · Pancreaticojejunostomy · Pancreatic fistula · Randomized controlled trial

Registration This trial is registered in the German Clinical Trials Register (trial ID DRKS00000419), initial trial registration as UKF000532 on March 15, 2006.

Funding This trial has been financed from institutional sources. Analysis of this trial was in part supported by financial support of the German Research Foundation (DFG) for the RECOPANC trial (DFG Ho 810/3-1).

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Introduction

Two main techniques are widely applied for the reconstruction of pancreatic juice drainage into the gastrointestinal tract after pancreatoduodenectomy, namely pancreatogastrostomy (PG) and pancreaticojejunostomy (PJ). Interestingly enough, this question was first addressed by Kausch in the first description of pancreatoduodenectomy in 1912[1] and remains a matter of debate until today.[2,3] The development of pancreatic fistula after pancreatoduodenectomy is associated with increased perioperative mortality[4,5] and in case of cancer with limited or reduced access to adjuvant therapy.[6] Pancreatic fistula in addition is associated with increased overall morbidity,[4,7] prolonged hospital stay, and readmission[4,8] as well as significantly increased healthcare costs.[7] The main goal for techniques of reconstruction after pancreatoduodenectomy is therefore avoiding leakage of pancreatic juice from the pancreatic anastomosis and development of postoperative pancreatic fistula (POPF). A

multitude of techniques for PG and PJ have been described[9]: Duct-to-mucosa anastomosis or invagination anastomosis, placement of a pancreatic duct stent, end-to-end or end-to-side pancreaticojejunostomy, use of an isolated intestinal loop for pancreatoenterostomy, and other details may vary between institutions and surgeons. There are numerous reports describing single techniques but only rarely have techniques been compared in the setting of a randomized controlled trial (RCT).[10] While almost all retrospective studies comparing PG and PJ suggest a reduction of POPF by PG,[10] up to now only one of four RCTs[3,11–13] comparing these two techniques demonstrated a statistically significant reduction of POPF with PG.

Inspired by retrospective observations of a reduced incidence of POPF with PG vs PJ, we conducted a single-center RCT to compare the two prevailing pancreatoenterostomy techniques performed at our institution: invagination pancreatogastrostomy with pursestring suture and duct-to-mucosa pancreaticojejunostomy according to the technique attributed to Warren and Catell.[14] A reduction of POPF rates was expected to be especially pronounced in high-risk patients with a soft pancreas.

Methods

Trial Design

The trial was designed as a single-institutional, open, randomized controlled study with two arms. The intervention arm was defined as pancreatogastrostomy, while pancreaticojejunostomy served as the control arm. The trial was approved by the institutional ethics committee of the University of Freiburg (vote number EK93/05).

Participants

Inclusion criteria were planned elective pancreatoduodenectomy (PD) for tumors or chronic pancreatitis and age of at least 18 years. Preoperative exclusion criteria were neoadjuvant or preoperative radio- or chemotherapy or both, treatment with high doses of corticosteroids (over 7.5 mg prednisone equivalent), previous operations within 1 week before PD (except laparoscopic staging) and advanced liver cirrhosis (Child-Pugh stage B or C). Intraoperative exclusion criteria were: pancreatoduodenectomy not performed (local inoperability or metastases or other resection procedures), PG, or PJ strongly preferred by the surgeon for technical reasons (e.g., extended resection of the pancreatic tail often in combination with portal vein resection, not allowing reconstruction via pancreatogastrostomy, or main pancreatic duct too small for duct–mucosa PJ). Patients were screened the day before operation, and written informed consent was obtained from all patients. All operations were performed by or with assistance of three experienced pancreatic surgeons. Demographic data, comorbidities, and relevant risk factors for POPF were assessed.

Interventions and Standard Treatment

Invagination intraluminal pancreatogastrostomy as formerly described by our group[15] and similarly by others[16,17] was defined as the trial intervention (Fig. 1): The pancreatic remnant was mobilized over 2–3 cm for adequate invagination into the stomach. An anterior gastrotomy of 8–10 cm was performed by electrocautery, and the posterior wall of the stomach was opened over 1–2 cm for the PG, which was secured by a running intragastrally placed pursestring suture (PDS 2-0 monofliament) in the gastric wall and a second internal line of interrupted seromuscular sutures between pancreatic capsule and stomach (PDS 4-0 monofilament). The anterior gastrotomy was then closed by running suture (PDS 4-0 monofilament).

Pancreaticojejunostomy was performed as described by Warren and Cattell[14] by duct-to-mucosa anastomosis and placement of a pancreatic duct drain (Peter Pflugbeil GmbH, Munich, Germany) that was exteriorized 15 cm aboral of the pancreaticojejunostomy via jejunopexia (Fig. 2).

During each operation, two soft capillary silicone drains (WEB-SIL Easy Flow Drainage ™, Websinger GmbH, Wolkersdorf, Austria) were placed directly adjacent to the pancreatoenteric anastomosis and two additional drains next to the hepaticojejunostomy. The patients received a standard postoperative treatment as previously described.[18] Part of the routine postoperative workup were daily amylase activity measurements from the peritoneal drain fluid at least until postoperative day 3 and before removal of drains. In

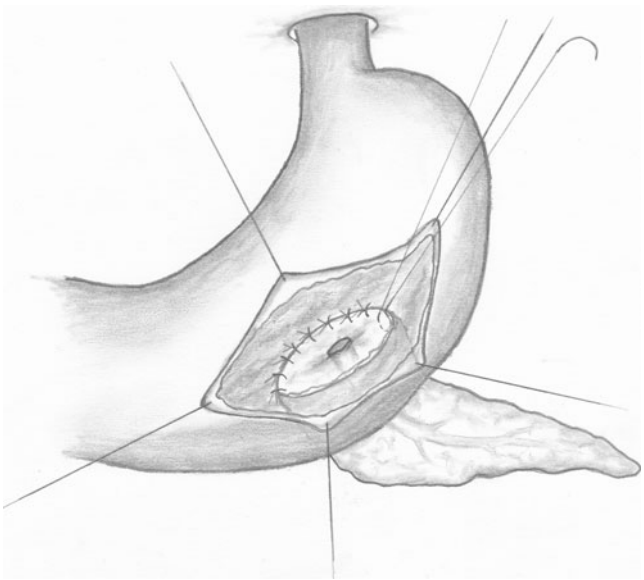

Fig. 1 Technique of pancreatogastrostomy

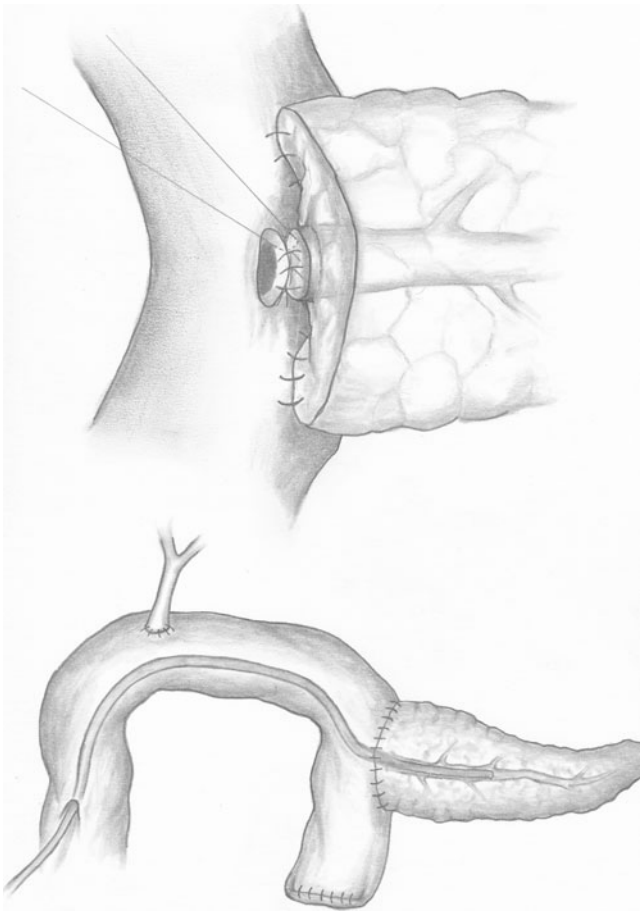

Fig. 2 Technique of pancreaticojejunostomy

addition, amylase activity was measured from every clinically suspicious drain fluid and from every newly inserted percutaneous drain. The abdominal drains were removed on postoperative day 5 if drain effluent and clinical course were unsuspicious and amylase activity was below 1,000 U/l, otherwise drains were left in place. In case of putrid drain fluid or high amylase activity, drains were removed stepwise over several days, under continuous clinical and laboratory assessment. Antibiotic treatment was initiated if there were signs of systemic inflammation.

Definitions

The primary endpoint of this study was the development of postoperative pancreatic fistula (POPF) of grade B or C according to the International Study Group of Pancreatic Surgery (ISGPS) definition,[19] with the modification that octreotide application was not used as a criterion for grade B or C POPF, as it was applied not only therapeutically for cases with POPF but also prophylactically if the surgeon felt that the pancreatoenteric anastomosis was at risk for POPF or when drain amylase activity was higher than 1,000 U/ml on postoperative day 3. Secondary endpoints were delayed gastric emptying (DGE) and bleeding (postpancreatectomy hemorrhage, PPH) as defined by the ISGPS definition.[20,21] As ISGPS definitions for DGE and PPH were published after the start of the trial, those were adapted during the course of the trial. In addition, intraabdominal fluid collection requiring invasive treatment, reoperation, mortality, operation time, and overall hospital stay were recorded. The size of the pancreatic duct was measured after resection in the remnant of the pancreas, and a duct diameter of less than 3 mm was defined as small. The judgement of the texture of the organ (soft/hard) was evaluated by the experienced pancreatic surgeon during the operation and later confirmed in the determination of the degree of fibrosis in histopathological analysis. We could previously demonstrate that subjective judgment of the pancreatic texture by the surgeon is very accurate concerning correlation to histopathologic grade of pancreatic fibrosis and especially valuable as a risk factor of POPF[18] and again aimed to confirm this.

Further assessed risk factors and secondary endpoints were intraoperative blood transfusion (transfusion requirement for any amount of packed red cells), intraabdominal fluid collection (fluid collection requring invasive treatment or operation), reoperation (reoperation at any time during hospital stay), operation time (from skin incision to skin closure), hospital stay (days from operation to hospital discharge), and mortality (due to any cause during hospital stay or 90 days after operation).

Sample Size

The sample size was calculated from the most recent and largest retrospective study available when the trial was initiated, suggesting a POPF rate of 2.3 % for PG and 20.4 % for control (PJ).[22] The calculations were performed with the PS software.[23] At a significance level of 5 % and power of 80 %, a necessary sample size of $n=58$ per study arm for the two-sided Fisher's exact test was calculated, giving a total number of $n=116$ subjects to be allocated and analyzed in the trial.

Randomization

The randomization sequence was generated by application of the random allocation rule[24,25] to $n=120$ concealed envelopes to preserve unpredictability until the end of the trial, leading to slightly uneven group size when $n=116$ subjects were randomized. Randomization was performed by opening one concealed envelope after finishing the resection procedure and ruling out intraoperative exclusion criteria.

Statistical Methods

After successful inclusion of $n=58$ patients, an interim analysis of the primary endpoint was performed in order to ensure security of the procedures. The primary endpoint (POPF B/C,

yes or no) in the two study arms PG and PJ was compared and tested for significance by two-sided Fisher's exact test. A stopping rule at $p<0.003$ for the interim analysis and the significance level $p<0.047$ for the final analysis were calculated using the WinLD software (http://www.biostat.wisc.edu/landemets/, University of Wisconsin, USA) according to an alpha-spending function of the O'Brien-Fleming type.[26] The interim analysis did not fulfill the stopping rule; therefore, the trial was continued as planned.[27] For the final statistical analysis, a planned subgroup analysis of the primary endpoint was performed for patients with a soft pancreas which constitute a high-risk population.[5,18,28] The intention-to-treat principle was applied for final analysis.

Secondary endpoints in the final analysis as well as patients' baseline characteristics were tested between treatment groups by two-sided Fisher's exact test for dichotomous variables and two-sided Mann–Whitney *U* test for continuous variables at significance level of $p<0.05$, respectively. SPSS version 17 (SPSS Inc, Chicago, USA) was used for statistical testing and exploratory data analysis.

Results

Recruitment, Participant Flow, and Numbers Analyzed

The trial flow diagram is shown in Fig. 3. Of $n=267$ patients screened, $n=116$ were randomized, all of whom completed the trial. There was one subject in whom the treatment assigned by randomization (PG) could not be performed for technical reasons. Reasons for exclusion of 126 patients (43 %) were patient declined to participate ($n=25/9$ %), patient meeting preoperative exclusion criteria ($n=10/4$ %), no resection due to locally advanced disease or distant metastasis ($n=47/18$ %), intraoperative technical preference of PG or PJ by the operating surgeon ($n=40/15$ %), and intraoperative decision to perform pancreatic resection other than pancreatoduodenectomy ($n=27/10$ %).

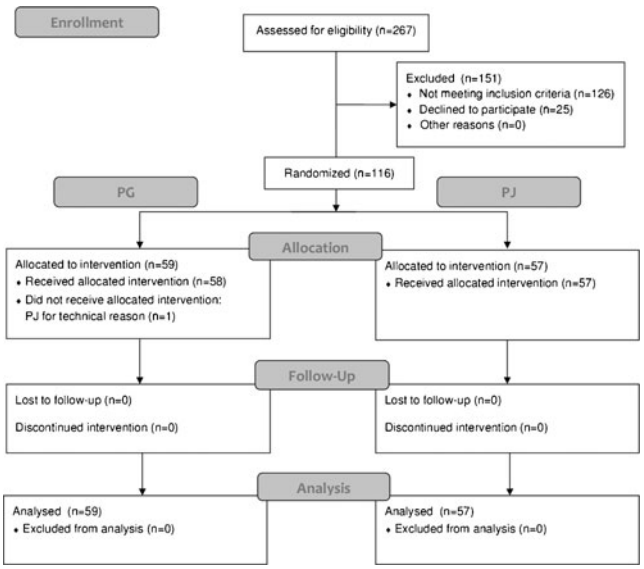

Fig. 3 Trial flow diagram. *PG* pancreatogastrostomy, *PJ* pancreaticojejunostomy

Patients and Operations

Baseline data of the patient collective are shown in Table 1. The treatment arms were balanced concerning demography and comorbidities. Pancreatic cancer was the most prevalent underlying disease, but also rare pathologies were represented in the study population. The usual resection technique was a pylorus-preserving pancreatoduodenectomy with standard lymphadenectomy. There were only 9 (8 %) classic Whipple operations and 18 (16 %) extended lymphadenectomies on the left side of the mesentericoportal axis due to large tumors extending to this area. Portal venous resection was performed routinely when suspicion of macroscopic infiltration of the mesentericoportal axis was present ($n=26$, 22 %). As octreotide treatment was used therapeutically but also prophylactically, in total 35 patients received octreotide (PG vs PJ, 22 vs 13, p=n.s.).

Relevant risk factors for POPF as identified by us and others[5,18,28,29] were balanced in the treatment arms as there were no statistically significant differences regarding gender,[30] age,[18] BMI,[18,31] prevalence of diabetes mellitus,[30] smoking[18] and cardiovascular disease,[30,32] histopathology,[18] frequency of soft pancreatic texture,[18] a small MPD,[18,28] intraoperative blood transfusions,[28,30] and extent of lymphadenectomy[30] (Table 1). A soft pancreas, previously demonstrated to be the most important risk factor by us and others,[18,30] was noted in $n=64$ patients (55 %), who were defined as the high-risk subgroup.

Analysis of the Primary Endpoint

Analysis of the primary endpoint is depicted in Table 2. POPF B/C occurred in 13 (11 %) patients out of the total trial population. All but one of these POPF occurred in the high-risk subpopulation with a soft pancreas. There was no significant difference in the incidence of POPF after PG or PJ in the total study population (PG vs PJ, 10 vs. 12 %, p= n.s.). Analysis of the high-risk subgroup with a soft pancreas ($n=64$) disclosed a reduced rate of POPF B/C with PG, without reaching the significance level (PG vs. PJ, 14 vs. 24 %, $p=0.352$).

Analysis of Secondary Endpoints

Results of secondary outcome analysis are shown in Table 3. Operation time was significantly shorter for pancreatoduodenectomies with PG by about 40 min in median (PG vs. PJ,

Table 1 Patients, operations, and risk factors

Parameter	All patients	PG	PJ	*p*
N	116	59	57	–
Demography and comorbidities				
Age (years)	66 (23–84)	67 (34–84)	64 (23–81)	0.573
Gender (m:f)	56:60	27:32	29:28	0.710
BMI (kg/m²)	24 (16–35)	24 (16–35)	23 (16–34)	0.387
ERD	58 (50 %)	28 (48 %)	30 (53 %)	0.710
IDDM	13 (11 %)	5 (9 %)	8 (14 %)	0.390
Renal disease	6 (5 %)	4 (7 %)	2 (4 %)	0.679
Cardiovascular disease	22 (19 %)	9 (16 %)	13 (23 %)	0.349
Pulmonary disease	13 (11 %)	6 (10 %)	7 (12 %)	0.775
Active smoker	34 (29 %)	19 (32 %)	15 (26 %)	0.544
Alcohol abuse	10 (9 %)	5 (9 %)	5 (9 %)	1.000
ASA I/II	81 (70 %)	42 (71 %)	39 (68 %)	0.836
Histopathology				
Pancreatic cancer	56 (48 %)	26 (44 %)	30 (53 %)	0.457
Chronic pancreatitis	18 (16 %)	8 (14 %)	10 (18 %)	0.614
Ampullary cancer	16 (14 %)	9 (15 %)	7 (12 %)	0.789
Bile duct cancer	4 (3 %)	2 (3 %)	2 (4 %)	1.000
Duodenal cancer	5 (4 %)	3 (5 %)	2 (4 %)	1.000
NEN	6 (5 %)	4 (7 %)	2 (4 %)	0.679
CNP	5 (4 %)	2 (3 %)	3 (5 %)	0.677
Other	6 (5 %)	5 (9 %)	1 (2 %)	0.207
Operations and intraoperative risk factors				
Classic Whipple-OP	9 (8 %)	7 (12 %)	2 (4 %)	0.163
Portal venous resection	26 (22 %)	11 (19 %)	15 (26 %)	0.377
Extended LAD	18 (16 %)	7 (12 %)	11 (19 %)	0.312
Soft pancreas	64 (55 %)	35 (59 %)	29 (51 %)	0.455
Small MPD	44 (38 %)	26 (44 %)	18 (32 %)	0.185
IntraOP transfusion	18 (16 %)	9 (15 %)	9 (16 %)	1.000

Values given as number (percentage of group total) or median (range), *p* value derived from two-sided Mann–Whittney test or Fisher's exact test

PG pancreatogastrostomy, *PJ* pancreaticojejunostomy, *BMI* body mass index, *ERD* endoscopic retrograde drainage, *IDDM* insulin-dependent diabetes mellitus, *NEN* neuroendocrine neoplasia, *CNP* cystic neoplasm of the pancreas, *LAD* lymphadenectomy, *MPD* main pancreatic duct, *OP operation*

Table 2 Analysis of the primary endpoint

Parameter	All patients	PG	PJ	*p*
Total trial population				
N	116	59	57	–
POPF B/C	13 (11 %)	6 (10 %)	7 (12 %)	0.775
High-risk subgroup (soft pancreas)				
N	64	35	29	–
POPF B/C	12 (19 %)	5 (14 %)	7 (24 %)	0.352
Low-risk subgroup (hard pancreas)				
N	52	23	28	–
POPF B/C	1 (2 %)	1 (4 %)	0 (0 %)	0.462

Values given as number (percentage of group total), *p* value derived from two-sided Fisher's exact test

PG pancreatogastrostomy, *PJ* pancreaticojejunostomy, *POPF B/C* postoperative pancreatic fistula of grade B or C according to the ISGPS definition

404 vs. 443 min, $p=0.005$). Hospital stay was non-significantly shorter with PG (PG vs. PJ, 15 vs. 17 days, $p=0.155$). Clinically relevant DGE of grade B or C was more frequent with PG, again not reaching significance (PG vs PJ, 27 vs 17 %, $p=0.246$). While the rate of postoperative bleeding events in total could be considered equal after PG and PJ (10 % vs 7 %, $p=0.743$), intraluminal bleeding was noted more often with PG (PG vs PJ, 7 vs 2 %), although this difference again was not statistically different.

As in our preceding retrospective analysis[15] that intraluminal bleeding after PG with a rate of 11 % was a clinically important problem, we addressed this complication very thoroughly in all patients of this study. One patient had reoperation because of bleeding into the stomach. In all other cases, this problem could be managed conservatively. No case of intraluminal PPH was life-threatening or causally associated with mortality.

Overall reoperation rate was 10 % ($n=11$) with the following indications for reoperations: intraabdominal fluid

Table 3 Analysis of secondary endpoints

Parameter		All patients	PG	PJ	*p*
N		116	59	57	–
DGE B/C[a]		23 (22 %)	14 (27 %)	9 (17 %)	0.246
PPH	Total	10 (9 %)	6 (10 %)	4 (7 %)	0.743
	Grade B/C	3 (3 %)	2 (3 %)	1 (2 %)	1.000
	Extraluminal	4 (3 %)	1 (2 %)	3 (5 %)	0.360
	Intraluminal	5 (4 %)	4 (7 %)	1 (2 %)	0.364
Fluid collection		10 (9 %)	7 (12 %)	3 (5 %)	0.322
Reoperation		11 (10 %)	7 (12 %)	4 (7 %)	0.529
Mortality		2 (2 %)	1 (2 %)	1 (2 %)	1.000
Operation time (min)		429 (230–683)	404 (280–629)	443 (230–683)	0.005
Hospital stay (days)		16 (7–135)	15 (7–135)	17 (10–60)	0.155

Values given as number (percentage of group total), *p* value derived from two-sided Fisher's exact test

PG pancreatogastrostomy, *PJ* pancreaticojejunostomy, *POPF* postoperative pancreatic fistula, *DGE* delayed gastric emptying, *PPH* postpancreatectomy hemorrhage according to the ISGPS definition

[a] Only analyzed in patients without reoperation (n=105)

collection with signs of infection not amenable to percutaneous drainage (n=4), bleeding (n=3), disruption and anastomotic insufficiency of PJ (n=1), disruption and anastomotic insufficiency of hepaticojejunostomy (n=1), burst abdomen (n=1), and mesenteric ischemia (n=1). There was no significant difference between PG and PJ regarding the specific indications for relaparotomy. Mortality was below 2 % in both trial arms (n=1 in PG and PJ).

Discussion

Since the first successful pancreatoduodenectomy by Kausch in 1909 and its publication in 1912,[1] the question whether to perform PG or PJ for reconstruction after pancreatoduodenectomy remains under debate. Almost all retrospective studies have suggested a reduction of morbidity, mainly in terms of POPF, with PG. On the other hand, there are only four completed RCT to date that have compared PG and PJ in terms of perioperative morbidity.

The first RCT was published in 1995 by the Johns Hopkins group.[11] N=145 patients were randomized intraoperatively to PG or PJ performed as non-stented double-layer anastomosis. POPF rates according to a center-specific definition were not significantly different after PG and PJ (PG vs PJ, 12 vs 11 %, p=n.s.).

Two more RCT comparing PG and PJ were published in 2005. One was a single-center RCT from Verona[12] that concentrated on high-risk patients with a soft pancreas (n=151) by preoperative randomization and drop-out in case of a hard or histologically fibrotic pancreas. PG and PJ were performed as non-stented single-layer and single-layer or double-layer duct–mucosa anastomosis, respectively. The primary endpoint of "multiple surgical complications" occurred significantly less frequently with PG. Also, rates of DGE, intrabdominal fluid collections, and biliary fistula were significantly reduced with PG. However, the authors found no significant difference in the rate of POPF (PG vs PJ, 13 vs 16 %) employing a center-specific definition. A possible limitation of this study was the center-specific definition of POPF where POPF had to be confirmed by fistulography. It is questionable that fistulography is sufficient to identify all POPF, and fistulography is neither mandatory nor recommended in the current ISGPS criteria.[19] Furthermore, there was an unusually high incidence of "biliary" and "enteric" fistulae (6–9 %) with overlap to pancreatic fistulae, which makes it possible that some of these were indeed POPF. As the rate of intraabdominal fluid collections was significantly higher with PJ in this trial, it is important to note that a considerable percentage of POPF have a "latent" presentation,[33,34] often as intraabdominal collections. These POPF may go unrecognized if amylase is not measured routinely from all drainage secretions.

Another RCT was conducted as a multicenter trial in France by Duffas and coauthors,[13] applying intraoperative randomization to PG or PJ without restrictions regarding technique. This trial did not demonstrate significant differences concerning POPF (PG vs PJ, 16 vs 20 %, defined either chemically or clinically). In addition, there was no difference in the number or severity of intraabdominal complications. A relatively high mortality (11 %) was attributed to inclusion of low-volume centers, a strong center-effect and inclusion of extended resections. The center contributing most of the patients to this trial had an overall mortality of 26 %, questioning the experience with both forms of pancreatic reconstruction in this trial.

All previously discussed trials employed a different definition of POPF, which limits comparability. Only later RCTs and retrospective studies have used the international consensus definition published in 2005 by the ISGPS.

The most recent RCT was reported from Barcelona by Fernandez-Cruz in 2008.[3] This trial randomized n=105 patients to PG and PJ by double-layer internally stented duct-to-mucosa anastomoses. For PG, the authors used a previously non-described technique modified to include gastric partitioning and anastomosis to the partially separated segment of the larger curvature of the stomach. A significantly reduced rate of POPF grade B/C according to the ISGPS definition (PG vs PJ, 4 vs. 18 %) was found. In addition, significantly less intraabdominal fluid collections, gastric emptying, and overall complications were observed.

In our present RCT, we compared total invaginated intragastric PG compared to duct–mucosa PJ for the reconstruction after pancreatogastrostomy at a single institution. The trial was inspired by retrospective studies including our own[15,35] suggesting a reduced POPF rate with PG especially for the "unfriendly" soft pancreas. From the results of the largest and most recent retrospective trial available at the time of initiation of our trial,[22] a total case number of $n=116$ patients was calculated for the primary endpoint clinically relevant POPF (grade B/C according to ISGPS). The study population comprised patients scheduled for elective pancreatoduodenectomy, and randomization was performed intraoperatively. Given the experience from previous published RCTs, we aimed to overcome some of the aforementioned limitations. The available ISGPS criteria were applied for the definitions of primary and secondary outcome measures. Care was taken to identify every POPF by means of routine daily measurement of drain amylase at least until postoperative day 3 and before drain removal. In addition, drain output of every percutaneous drain or puncture fluid was assessed for amylase content. To avoid a bias by surgeon experience, the trial was performed at a high-volume academic center and all operations in this study were performed by three surgeons with a personal experience of over 300 pancreatic resections. Known risk factors for POPF were assessed, among them pancreatic texture as one of the strongest predictors of POPF.

Analysis of the primary endpoint did not show a statistically relevant difference in POPF rates between PG and PJ. There are some potential confounding factors to be mentioned that may have contributed to a lower overall POPF rate, with differences in outcome becoming increasingly difficult to detect by statistical tests. First, the overall incidence of POPF was lower than in our retrospective study (RCT vs retrospective study, 11 vs 17 %), which may represent a continuing learning curve even after a long-term center experience in pancreatic surgery. Second, there may be a selection bias derived from the intraoperative randomization process: as randomization was done only if the surgeon felt that both methods (PG and duct–mucosa PJ) would be technically well applicable, a certain number of high-risk cases, for example with soft pancreas and small MPD may have been excluded in favor of performing a PG, which has been established as the preferred reconstruction technique among all surgeons of our team. Third, recently, three RCTs[31,36,37] and a metaanalysis[38] have shown a significant reduction of POPF rates with external MPD stenting in PJ as well as PG. The addition of an external stent in PJ but not in PG in our RCT is therefore potentially confounding as it may have reduced the POPF rate in the control group. Our own previous data did however not demonstrate a reduction of POPF rates with external stenting in PJ.[15]

It should be noted that an RCT comparing early (day 3) and late (day 5) removal of abdominal drains after PD demonstrated a significant reduction of POPF with early drain removal.[39] As drains were not removed before day 5 in our trial, this factor may be ruled out as a confounder. Octreotide treatment was used therapeutically for POPF but also prophylactically in our trial. As criteria for application were universal without statistical difference in the trial arms and efficacy in prevention of POPF is questionable,[40,41] we do not regard this as a confounding factor.

A soft pancreas, as defined by intraoperative palpation has been identified as the strongest single risk factor for POPF by us and others.[18,28] A soft parenchyma is associated with a well-preserved exocrine pancreatic function,[42–45] making the pancreatoenteric anastomosis prone to POPF by higher fluid output and exposure to digestive enzymes. Intraoperative assessment of pancreatic texture by the experienced surgeon is only a qualitative and subjective, yet valid parameter. Hard pancreatic texture has been shown to correlate with histologic grade of pancreatic fibrosis and is strongly associated with chronic pancreatitis (chronic fibrosing inflammation) and pancreatic ductal adenocarcinoma (obstructive fibrosing pancreatitis).[18,28,30,46–48] Vice versa, a soft parenchyma is associated with other pathologies—ampullary cancer, distal bile duct cancer, neuroendocrine tumors, and cystic neoplasms of the pancreas.[18,28,30,46–48] In addition, a "fatty pancreas" has been reported to be prone to POPF formation and is probably soft; however, a correlation to palpation was not tested.[49]

Based on these observations, we defined a subgroup of high-risk patients by the intraoperative finding of a soft pancreas. In accordance, all but one POPF of grade B/C occurred in this high-risk group. POPF rate in this group was reduced to nearly one half with PG (24 vs 14 % with PJ). This difference did however not reach significance. It is nevertheless noteworthy as it confirms our retrospective data suggesting reduced POPF rate with PG, as well as the RCT from Verona[12] which included only subjects with soft pancreas and found a reduced morbidity with PG. Some theoretical considerations can support these findings.

Besides offering a deeper invagination of the pancreatic remnant than duct–mucosa PJ, an advantage of PG may be prevention of activation of pancreatic juice next to the anastomotic site: At a low pH[50] and in the absence of enterokinase in the stomach,[51,52] pancreatic digestive enzymes remain inactivated. Even though these theoretical considerations have driven us to perform this study, we were not able to demonstrate superiority of either anastomosis in prevention of pancreatic fistula.

Some authors have advocated PG for patients with IPMN because endoscopic surveillance of the pancreatic resection margin for recurrence is possible by inspection, endoscopic ultrasound, and eventually endoscopic retrograde pancreatography.[53–56] Magnetic resonance cholangiopancreatography (MRCP) is in our experience a very sensitive method for detection of cystic lesions of the pancreas or

pancreatic duct irregularities, also in the setting of postoperative follow-up. We do not perform routine endoscopy during follow-up. One patient included in this trial had a marked dilatation of the MPD during follow-up after PD for IPMN; however, endoscopy did not disclose signs of recurrent IPMN.

Regarding secondary endpoints, this RCT again confirms retrospective studies by us and others[15,16] showing increased intraluminal bleeding with PG. Most intraluminal bleeding was of PPH grade A (no specific intervention required), and the incidence has declined when compared to our previous study[15] (from 11 to 7 %). The latter may be explained by a learning effect involving refined hemostatic measures using no thermocoagulation and only 5-0 monofilamant sutures at the cut surface of the remaining pancreatic tail.[15] For extraluminal bleeding, generally associated with the development of pancreatic fistula, we found a significant association with mortality, highlighting the severity of this complication and the relevance of fistula formation after pancreatic resection.

DGE rate was not significantly different with PG or PJ in this trial. Possible factors that might contribute to increased DGE in general after pancreatogastrostmy might be increased gastral paresis and pylorospasm due to extended denervation by increased operative trauma (two gastrotomies), as well as retroperitoneal fixation of the stomach by the invaginated pancreas.[15,16] DGE might contribute to a prolongation of hospital stay; however, median hospital stay was shorter with PG, not reaching statistical significance.

Operation time was significantly shorter for PG, which is likely due to the technically far less demanding anastomotic technique.

Conclusion

In summary, our current RCT did not demonstrate a significant reduction of POPF with PG vs PJ. Failure to reach statistical significance may be attributed to a relatively low case number and negative selection of high-risk subjects by intraoperative randomization. PG can be performed in a shorter operation time; however, our trial also disclosed a non-significantly increased rate of intraluminal bleeding. Evaluating the advantages vs the list of disadvantages of PG, it may be a method to be evaluated for reconstruction in pancreatoduodenectomy, especially for the high-risk pancreas. Recently, a multicenter observer blinded RCT (RECOPANC, DRKS00000767, U1111-1117-9588) for the comparison of PG and PJ has been initiated in Germany to overcome the aforementioned limitations of previous RCTs and find a final and definite answer.

Acknowledgments We thank Joachim Wellner, MD for the artwork of this article.

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