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Pancreatogastrostomy Versus Pancreatojejunostomy for RECOnstruction After PANCreatoduodenectomy (RECOPANC, DRKS 00000767)

Perioperative and Long-term Results of a Multicenter Randomized Controlled Trial

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Objectives: To assess pancreatic fistula rate and secondary endpoints after pancreatogastrostomy (PG) versus pancreatojejunostomy (PJ) for reconstruction in pancreatoduodenectomy in the setting of a multicenter randomized controlled trial.

Background: PJ and PG are established methods for reconstruction in pancreatoduodenectomy. Recent prospective trials suggest superiority of the PG regarding perioperative complications.

Methods: A multicenter prospective randomized controlled trial comparing PG with PJ was conducted involving 14 German high-volume academic centers for pancreatic surgery. The primary endpoint was clinically relevant postoperative pancreatic fistula. Secondary endpoints comprised perioperative outcome and pancreatic function and quality of life measured at 6 and 12 months of follow-up.

Results: From May 2011 to December 2012, 440 patients were randomized, and 320 were included in the intention-to-treat analysis. There was no significant difference in the rate of grade B/C fistula after PG versus PJ (20% vs 22%, $P = 0.617$). The overall incidence of grade B/C fistula was 21%, and the in-hospital mortality was 6%. Multivariate analysis of the primary endpoint disclosed soft pancreatic texture (odds ratio: 2.1, $P = 0.016$) as the only independent risk factor. Compared with PJ, PG was associated with an increased rate of grade A/B bleeding events, perioperative stroke, less enzyme supplementation at 6 months, and improved results in some quality of life parameters.

Conclusions: The rate of grade B/C fistula after PG versus PJ was not different. There were more postoperative bleeding events with PG. Perioperative morbidity and mortality of pancreatoduodenectomy seem to be underestimated, even in the high-volume center setting.

Keywords: pancreatoduodenectomy, pancreatogastrostomy, pancreatojejunostomy, postoperative pancreatic fistula, postoperative pancreatic function

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The first successful pancreatoduodenectomy was performed as a 2-stage procedure by Walter Kausch in 1909.[1] Later, Allen O. Whipple popularized the procedure by a series of 37 pancreatoduodenectomies during his career.[2] Because of high mortality, the operation was nearly abandoned in the 1970 s.[2] In the 1990 s, large retrospective series from specialized centers around the world set a benchmark for operative mortality of below 5%.[2] Nevertheless, morbidity remains substantial after pancreatoduodenectomy.[3–10] The main contributing factor is postoperative pancreatic fistula (POPF), involving leakage of pancreatic juice from the pancreatic anastomosis, which can lead to severe secondary complications such as intra-abdominal abscesses and erosion bleeding.[9,11,12] Data regarding the prevention of POPF by application of somatostatin analogues have been controversial thus far,[13,14] but a recent

randomized trial strongly suggests that pasireotide successfully reduces POPF rates.[15] Numerous attempts at improving pancreatic anastomosis techniques to lower POPF rates have been proposed.[2,16,17] The hypothesis of this trial dates back to Walter Kausch, who discussed the possibility of anastomosis of the pancreatic remnant to the jejunum (pancreatojejunostomy, PJ) or the stomach (pancreatogastrostomy, PG) in his 1912 original publication of the first successful pancreatoduodenectomy.[1]

Almost all retrospective studies suggest superiority of PG over PJ in terms of reduced POPF and other complications.[18] To date, however, conflicting results have been reported from 8 prospective randomized controlled trials (RCTs) published from 1995 to 2014[19–26] (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778): Only 3 RCTs[22,24,25] have demonstrated a reduced rate of POPF after PG, and 4 RCTs[20,22,24,25] found advantages of PG over PJ in terms of postoperative complications. Soft pancreatic texture was identified as a risk factor for POPF and other complications in 4 RCTs.[19,21,23,25] However, the available RCTs have some limitations. With the exception of the recent Belgian multicenter RCT [24] including 329 patients, total case numbers of the RCTs are relatively low (n = 90–151) and only 2 RCTs are multicenter trials. Definitions of perioperative outcomes vary as early trials did not use the current consensus definitions of specific complications in pancreatic surgery established by the International Study Group for Pancreatic Surgery (ISGPS). Although many technical variations of PG and PJ have been reported,[16,17] all 8 RCTs were restricted to specific subtypes of PG and PJ. Only 2 RCTs with contradictory results report on postoperative pancreatic function measured during follow-up of 3 to 12 months: the Egyptian trial[26] reports worse and the Spanish trial[25] reports better pancreatic function. None of the RCTs report on quality of life during follow-up.

Here we present data collected at 14 high-volume centers for pancreatic surgery in Germany from the currently largest multicenter randomized trial comparing PG with PJ with respect to perioperative complications and long-term pancreatic function and quality of life.

PATIENTS AND METHODS

Study Design, Hypothesis, and Inclusion Criteria

The RECOnstruction after PANCreatoduodenectomy Study (RECOPANC) was designed as a randomized, controlled, observer- and patient-blinded multicenter trial with 2 parallel treatment arms (PG and PJ) (see Supplemental Digital Content, available at http://links.lww.com/SLA/A774). The hypothesis was that the rate of clinically relevant POPF is lower after PG. Inclusion criteria were planned pancreatoduodenectomy at one of the participating academic centers and age more than 18 years. Exclusion criteria were participation in interfering clinical trials and expected lack of compliance. With the rationale to increase willingness of participating surgeons to recruit patients and to achieve greater generalizability of the results, we did not restrict PG or PJ to a special technique. Fourteen German academic centers (RECOPANC Trial Group[27]) with a median case load of 78 major pancreatic resections per year (range: 29–499, figures for year 2012 from the Association of German University Clinics, http://www.uniklinika.de) participated in the trial.

Primary Endpoint and Sample Size

POPF is defined by ISGPS as the occurrence of amylase activity in abdominal drain fluid of 3 times the upper serum limit on postoperative day 3 or later.[28,29] In brief, grade A fistula is self-limited and does not need specific treatment, grade B requires medical or invasive interventional treatment, and grade C leads to reoperation and/or severe secondary complications. The primary endpoint chosen for this trial was clinically relevant POPF, that is, ISGPS grade B or C, with the modification that application of somatostatin analogues was not considered a criterion for grading. The primary endpoint was assessed on postoperative day 3 at hospital discharge and on postoperative day 30 to detect all POPFs.

Based on the prior assumption of a POPF B/C rate of 6% and 16% with PG and PJ, respectively, $\alpha = 5\%$ and $\beta = 20\%$, a sample size of 153 per treatment arm (PG vs PJ) was calculated with the 2-sided χ^2 test. An adaptive interim analysis of the primary endpoint according to Bauer and Koehne[30] was planned after recruitment of 152 patients to allow for premature trial termination (with 1-sided stopping boundaries of $P < 0.0038$) and sample size recalculation.

Secondary Endpoints and Follow-up

Secondary surgical endpoints were death, relaparotomy, completion pancreatectomy, anastomotic leak other than pancreatic fistula, wound infection, delayed gastric emptying, postpancreatectomy hemorrhage according to the ISGPS definitions,[31,32] intra-abdominal abscess requiring invasive treatment, operation time (skin incision to skin closure), and postoperative hospital stay. Further secondary endpoints included septic shock, respiratory failure, deep venous thrombosis, lung embolism, myocardial infarction, and stroke. Pancreatic endocrine and exocrine functions and quality of life were evaluated in long-term follow-up at baseline, 6 and 12 months after the operation by the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) C30 and the pancreatic cancer module PAN26.[33,34]

Randomization and Blinding

Center-based block randomization was performed by the participating centers using a centralized Web-based tool (Randomizer Software, Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz, www.randomizer.at) with allocation concealment. To avoid a possible intraoperative selection of low-risk patients,[23] randomization was performed preoperatively. Obviously, the surgeons were not blinded concerning the intervention. Therefore, blinded observers at the participating centers assessed the primary endpoint. Patients were kept blinded regarding the intervention and unblinded only in the case of emergencies where necessary.

Ethical Approval, Safety, and Registration

The study protocol was approved by the local ethics committees of the participating centers and carried out according to the rules of Good Clinical Practice and the Declaration of Helsinki.[35] Written informed consent was obtained from each patient. An independent institution served as the Data Safety Monitoring Board and was responsible for on-site clinical monitoring, source data verification, and management of severe adverse event reports (Center for Clinical Studies, Freiburg, Germany). The trial was assigned a Universal Trial Number (UTN U1111-1117-9588) and registered in the German Trials Register (DRKS 00000767) on March 23, 2011. The study protocol was published in *Trials*.[27]

Statistical Analysis

The primary endpoint was analyzed according to the intention-to-treat principle (see Supplemental Digital Content, available at http://links.lww.com/SLA/A775). A multivariate logistic regression model adjusting a priori for age, center, surgeon volume/experience, and pancreatic texture was applied to compare POPF rates in both treatment groups. Missing values for the primary endpoint were replaced by imputed case analysis according to Higgins et al.[36] Exploratory analysis was planned for secondary endpoints. SAS software 9.1 (SAS 9.1 software, SAS, Cary NC) and 2-sided tests were used for all calculations.

RESULTS

Trial Flow

A total of 618 patients were screened and 440 patients were randomized from May 31, 2011, through December 5, 2012. The number of patients randomized per center is shown in Supplemental Digital Content Fig. S1, available at http://links.lww.com/SLA/A776, and ranged from 6 to 84, with 5 centers recruiting less than 20 patients and 2 centers recruiting more than 50 patients. After the interim analysis of the first 152 included patients, the Data Safety and Monitoring Board advised continuation of the trial. A total of 120 randomized patients were excluded from the final analysis: 3 patients were randomized by mistake (randomized but not eligible), 5 did not undergo laparotomy, and 112 did not receive pancreatoduodenectomy and were, therefore, excluded from further analysis. Fifteen patients randomized to PG received PJ and 12 patients randomized to PG received PJ because of the surgeon's technical preference. Reasons given for PJ instead of PG included technical problems with PG: short pancreatic remnant (n = 9), difficult pancreatic remnant mobilization (n = 2), and gastric ulcer (n = 1); reasons for PG instead of PJ were soft pancreas with small duct (n = 11) and pancreas divisum (n = 1). In total, 320 patients were included in the intention-to-treat analysis of the primary endpoint: 149 patients randomized for PJ and 171 randomized for PG. Ninety-six patients did not finish the whole 12-month follow-up because of prior death (n = 75), loss to follow-up (n = 10), withdrawal of consent (n = 5), and other reasons (n = 6) (Fig. 1).

Patient Baseline Characteristics and Operations

Patient baseline parameters are shown in Table 1. The treatment groups were balanced in terms of age, sex, body mass index, indications, symptoms, preoperative biliary drainage, comorbidities, American Society of Anesthesiologists (ASA) Classification, medication, and standard laboratory parameters. The treatment groups were also comparable in terms of operation technique, surgeon experience/volume, and blood loss/intraoperative transfusion requirement. In particular, the rates of soft pancreata (PG vs PJ, 59% vs 57%) and nondilated pancreatic ducts (PG vs PJ, 58% vs 55%), which are indicators for increased risk of fistula formation,[5,37–40] were not significantly different between the 2 groups (Table 1).

Supplemental Digital Content Table S2, available at http://links.lww.com/SLA/A779, shows the technical varieties used for PG and PJ at the trial centers. According to the ISGPS classification for pancreatic anastomoses,[16] the most commonly performed techniques were nonstented duct-mucosa anastomosis (ISGPS type I-A-S0) with 2 interrupted monofilament resorbable suture rows for PJ and nonstented dunking PG (ISGPS type II-B-S0) anastomosis with purse-string plus interrupted monofilament resorbable suture.

Primary Endpoint Analysis

The rate of clinically relevant POPF was 20% after PG and 22% after PJ in the control group ($P = 0.62$, 2-sided χ^2 test, Table 2). In a multivariate logistic regression model (Table 2), including anastomotic technique (PG vs PJ), age, center (north vs south), pancreatic texture (soft vs hard) and surgeon volume (pancreatic resections per year), and soft pancreatic texture was the only significant factor affecting POPF B/C, with an odds ratio estimate of 2.1 ($P = 0.016$) (Table 2).

As there were 12 patients allocated to PG receiving PJ instead and 15 patients with PG instead of PJ, we also performed an as-treated analysis of the primary endpoint (see Supplemental Digital Content Table S3, available at http://links.lww.com/SLA/A780). The results did not differ from those of the intention-to-treat analysis.

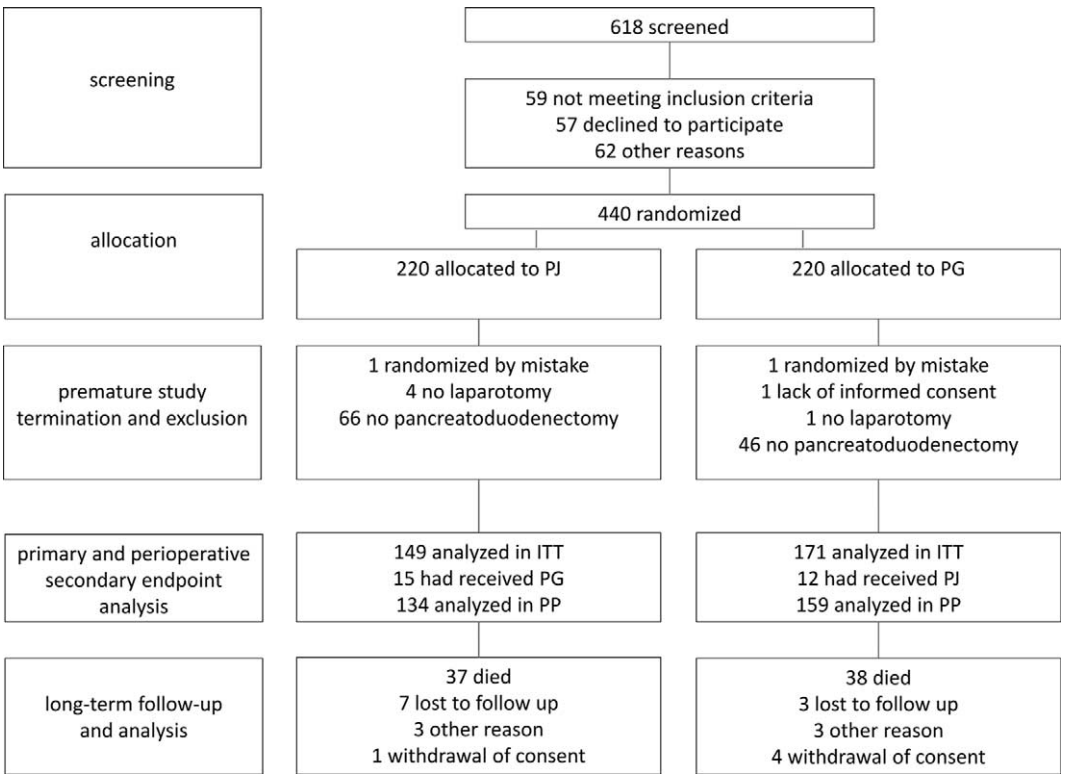

FIGURE 1. Trial flow chart. ITT indicates intention to treat; PP, per protocol.

TABLE 1. Patients, Baseline Parameters, and Operations

	PJ		PG		Total		
Parameter	**N or Median**	**% or Range**	**N or Median**	**% or Range**	**N or Median**	**% or Range**	***P***
Total	149		171		320		—
			Baseline Data				
Age, yr	66	29–87	68	35–86	68	29–87	0.787
Sex							
Male	93	62%	95	56%	188	59%	0.214
Female	56	38%	67	44%	132	41%	
BMI (kg/m^2)	25	15–43	25	16–39	25	15–43	0.706
Chronic pancreatitis	14	9%	14	8%	28	9%	
Pancreatic adenocarcinoma	98	66%	104	61%	202	63%	
Ampullary adenocarcinoma	11	7%	10	6%	21	7%	
Indications							0.695
CNP	4	3%	8	5%	12	4%	
NET	2	1%	3	2%	5	2%	
Other	20	13%	32	19%	52	16%	
Weight loss	89	60%	97	57%	186	58%	0.587
Symptoms							
Pain	79	53%	84	49%	163	51%	0.487
Jaundice	72	48%	88	52%	160	50%	0.575
Preop biliary drainage							
ERD	60	40%	61	36%	121	38%	0.396
PTD	4	3%	7	4%	11	3%	0.488
History of acute pancreatitis	20	13%	17	10%	37	12%	0.331
Chronic pancreatitis	40	27%	45	26%	85	27%	0.915
Prior abdominal surgery	69	46%	80	47%	149	47%	0.932
Cardiac	58	39%	68	40%	126	39%	0.878
pulmonary	14	9%	19	11%	33	10%	0.615
Comorbidities							
Renal	15	10%	15	9%	30	9%	0.692
Hepatic	9	6%	10	6%	19	6%	0.942
Ex-smoker	40	27%	33	19%	73	23%	0.074
Active smoker	44	30%	42	25%	86	27%	
Ex-alcohol abuse	17	11%	19	11%	36	11%	0.673
Active alcohol abuse	16	11%	24	14%	40	13%	
ASA							
I	14	10%	18	11%	32	10%	
II	81	56%	86	52%	167	53%	
III	50	34%	61	37%	111	36%	0.881
IV	1	1%	2	1%	3	1%	
NA	3	2%	4	2%	7	2%	
Medication							
Glucocorticoids	4	3%	3	2%	7	2%	0.570
Immunosuppressives	2	1%	1	1%	3	1%	0.483
Analgesics	29	20%	45	26%	74	23%	0.147
Somatostatin analog	2	1%	0	0%	2	1%	0.129
Neoadjuvant cx	4	3%	3	2%	7	2%	0.570
Neoadjuvant rx	2	1%	1	1%	3	1%	0.483
Laboratory							
Amylase [U/L]	51	13–360	58	9–536	56	9–536	0.168
Creatinine (μmol/L)	61	15–328	62	37–519	62	156–519	0.581
Bilirubin (μmol/L)	12	3–598	15	2–371	14	2–598	0.951
C-reactive protein (mg/L)	6	0–111	6	0–177	6	0–177	0.618
Total protein (g/L)	70	44–558	71	55–85	70	44–558	0.442
CA 19–9 (U/mL)	42	1–11,000	48	1–4,491	47	1–11,000	0.503
Hemoglobin (mmol/L)	8	4–10	8	4–10	8	4–10	0.418
Leukocytes (1000/mL)	7	3–18	7	3–19	7	3–19	0.436
Thrombocytes (1000/mL)	260	95–569	270	37–625	268	37–625	0.926
			Operations				
Surgeon experience*							
<5	29	20%	24	14%	53	17%	
5–10	50	34%	54	32%	104	33%	0.301
>10	69	47%	92	54%	161	51%	
NA	1	1%	1	1%	2	1%	
<10	13	9%	15	9%	28	9%	

(*Continued*)

TABLE 1. (*Continued*)

	PJ		PG		Total		
Parameter	**N or Median**	**% or Range**	**N or Median**	**% or Range**	**N or Median**	**% or Range**	***P***
Surgeon volume†							
10–25	43	29%	49	29%	92	29%	
>25	92	62%	106	62%	198	62%	0.999
NA	1	1%	1	1%	2	1%	
Technique							
PPPD	121	81%	134	78%	255	80%	0.528
Classic Whipple	28	19%	37	22%	65	20%	
NA	5	3%	11	6%	16	5%	
LAD							
Standard	106	71%	124	73%	230	72%	0.331
Extended	38	26%	36	21%	74	23%	
Portal venous resection	30	20%	29	17%	59	18%	0.465
Additional organ resection	39	26%	39	23%	78	24%	0.484
Blood loss	500	0–4,800	500	0–3,500	500	0–4,800	0.581
Intraoperative red blood cell transfusion							
No	132	89%	146	85%	278	87%	
1	3	2%	6	4%	9	3%	0.708
2	8	5%	13	8%	21	7%	
>2	6	6%	6	6%	12	12%	
Pancreatic texture							
Hard	62	43%	66	41%	128	42%	
Soft	83	57%	95	59%	178	58%	0.755
NA	4	3%	10	6%	14	4%	
MPD diameter							
Normal (≤3 mm)	78	55%	94	58%	172	56%	
Dilated (>3 mm)	64	45%	69	42%	133	44%	0.630
NA	7	5%	8	5%	15	5%	

P values derived from 2-sided χ^2 test and Student *t* test.

*Years of pancreatic surgery.

†Pancreatoduodenectomies per year.

ASA indicates American Society of Anesthesiologists; BMI, body mass index; CA, 19-9, Carbohydrate antigen 19-9; CNP, cystic neoplasm of the pancreas; cx, chemotherapy; ERD, endoscopic retrograde drainage; LAD, lymphadenectomy; MPD, main pancreatic duct; NA, not assessed; NET, neuroendocrine tumor; PPPD, pylorus preserving pancreatoduodenectomy; PTD, percutaneous transhepatic drainage; rx, radiotherapy.

Assessment of Learning Effects

The odds ratio estimate for fistula rate in surgeons with less than 10 pancreatoduodenectomies was 1.2 to 6.8 (95% confidence interval) but did not reach the significance level ($P = 0.064$ in multivariate analysis, see Table 2). Surgeons with less than 10 pancreatoduodenectomies per year had a higher fistula rate with PJ (46%) than with PG (27%), and this effect was gradually lost with increasing individual case load (see Supplemental Digital Content Table S4, available at http://links.lww.com/SLA/A781); however, these differences did not reach statistical significance. There was also no significant center effect as to the preferred type of anastomosis in the participating centers (see Supplemental Digital Content Table S4, available at http://links.lww.com/SLA/A781).

Perioperative Secondary Endpoint Analysis

Operation time did not differ between PG and PJ. There were no significant differences between PG and PJ with regard to the frequency of surgical complications such as delayed gastric emptying, intra-abdominal abscesses, relaparotomy, completion pancreatectomy, anastomotic leaks, and surgical site infection. There was also no difference in the incidence of systemic complications such as septic shock, respiratory failure, deep vein thrombosis, lung embolism, and myocardial infarction. There were more (n = 5) stroke events in the PG group but none in the PJ group ($P = 0.035$) and significantly more postpancreatectomy hemorrhage events in the PG group ($P = 0.023$), the latter due to more grade A (5% vs 1%) and B (9% vs 4%) hemorrhages. Stroke and grade A/B bleeding were not associated, however ($P = 0.998$). Perioperative in-house mortality in the treatment groups (PG vs PJ, 6% vs 5%, $P = 0.963$) and 90-day mortality (PG vs PJ, 10% vs 5%, $P = 0.167$) were not statistically different. Postoperative hospital stay was equal with a median of 16 days (Table 3).

Survival During Follow-up

Overall survival curves are given in Supplemental Digital Content Fig. S2, available at http://links.lww.com/SLA/A777. One-year (365 days) Kaplan-Meier survival estimates (±standard error) were 77% ± 3% in PG and 76% ± 4% in PJ and thus comparable ($P = 0.675$ in 2-sided log-rank test) (see Supplemental Digital Content Fig. S2, available at http://links.lww.com/SLA/A777).

Pancreatic Function and Long-term Follow-up

The percentage of patients receiving oral enzyme replacement rose from 8% preoperatively to around 80% during 6- and 12-month follow-up. Exploratory analysis also suggested a significantly reduced rate of oral enzyme replacement therapy in patients with PG at 6 months after the operation (PG vs PJ, 72% vs 89%, $P < 0.001$). This difference did not persist at 12-month follow-up because of a slightly decreasing percentage of PJ patients using oral enzyme supplementation (PG vs PJ, 72% vs 81%, $P = 0.11$). However, simultaneously the rate of patients reporting steatorrhea in the PJ group increased (from 17% at 6 months to 22% at 12 months), suggesting now insufficient enzyme supplementation in some patients. This was not the case with PG, where reported steatorrhea

TABLE 2. Primary Endpoint Analysis

		Univariate Analysis		
Parameter	**Total n**	**No/POPF A n (%)**	**POPF B/C n (%)**	***P***
All patients	320	253 (79%)	67 (21%)	—
PJ	149	116 (78%)	33 (22%)	0.617
PG	171	137 (80%)	34 (20%)	

	Multivariate Analysis			
Parameter	**Odds Ratio**	**Lower CI**	**Upper CI**	***P***
PG vs PJ	0.864	0.495	1.507	0.607
Age, yr	0.988	0.966	1.011	0.318
Soft vs hard pancreatic texture	2.094	1.145	3.827	0.016
Center location (north vs south)	1.048	0.58	1.896	0.876
Surgeon volume 10–25 vs >25 PD/yr	1.578	0.822	3.029	0.863
Surgeon volume <10 vs >25 PD/yr	2.801	1.155	6.794	0.064

P values derived from 2-sided χ^2 test (univariate) and binary logistic regression (multivariate).

CI indicates 95% confidence interval; PD, pancreatoduodenectomy; POPF, postoperative pancreatic fistula grade according to the International Study Group for Pancreatic Surgery definition.

TABLE 3. Perioperative Secondary Endpoint Analysis

	PJ		PG		Total		
Parameter	**N or Median**	**% or Range**	**N or Median**	**% or Range**	**N or Median**	**% or Range**	***P***
Total	149	171	320	—			
Operation time	337	165–565	332	165–600	332	165–600	0.706
DGE* (delayed gastric emptying)							
No	87	59%	107	63%	194	61%	
Grade A	39	27%	44	26%	83	26%	
Grade B	9	6%	14	8%	23	7%	0.301
Grade C	12	8%	6	4%	18	6%	
Missing	2		0		2		
PPH* (postpancreatectomy hemorrhage)							
No	132	89%	135	79%	167	83%	
Grade A	1	1%	9	5%	10	3%	
Grade B	6	4%	16	9%	22	7%	0.023
Grade C	10	7%	11	6%	21	7%	
IA with IPC drainage	19	13%	18	11%	37	12%	
IA with OP drainage	12	8%	15	9%	27	8%	0.814
Other surgical complications							
Relaparotomy completion	27	18%	20	12%	47	15%	0.100
Pancreatectomy	9	6%	6	4%	15	5%	0.285
Hepaticoenterostomy leak	5	3%	3	2%	8	3%	0.480
Gastroenterostomy leak	3	2%	6	4%	9	3%	0.511
SSI	18	12%	20	12%	28	12%	1.000
Systemic complications							
Septic shock	4	3%	6	4%	10	3%	0.672
Respiratory failure	8	6%	12	7%	20	7%	0.542
Deep vein thrombosis	1	1%	0	0%	1	0%	0.283
Lung embolism	2	1%	3	2%	5	2%	0.766
Myocardial infarction	1	1%	1	1%	2	1%	0.923
Stroke	0	0%	5	3%	5	2%	0.035
Missing	6		7		13		—
Postoperative hospital stay (d)	16	3–129	15	5–208	16	3–208	0.404
In-house mortality†	8/148	5%	10/169	6%	18/317	6%	0.963
90-d mortality‡	7/143	5%	16/165	10%	23/308	7%	0.167

P values derived from 2-sided χ^2 test, Student *t* test.

*According to the International Study Group for Pancreatic Surgery (ISGPS) definition.

†Missing data (n = 3) excluded.

‡Censored cases (n = 12) excluded.

DGE indicates delayed gastric emptying; IA, intra-abdominal abscess; IPC, interventional percutaneous; OP, operative; PPH, postpancreatectomy hemorrhage; SSI, surgical site infection requiring invasive treatment.

TABLE 4. Long-term Pancreatic Function

Pancreatic Function								
		PJ		PG		Total		
Time	Parameter	N or Median	% or Range	N or Median	% or Range	N or Median	% or Range	*P*
OP	Total patients in follow-up	149	171	320	—			
	Steatorrhea	23	15%	21	12%	44	14%	0.414
	OES	13	9%	14	8%	27	8%	0.863
	DM	35	24%	45	26%	80	25%	0.560
6 mo	Total patients in follow-up	122		143		265		—
	Steatorrhea	21	17%	28	20%	49	19%	0.621
	OES	108	89%	103	72%	211	80%	<0.001
	DM	38	31%	40	28%	78	29%	0.572
12 mo	Total patients in follow-up	101		122		223		—
	Steatorrhea	22	22%	16	13%	38	17%	0.092
	OES	82	81%	88	72%	170	76%	0.114
	DM	34	24%	35	29%	69	31%	0.424

Therapy Details									
			PJ		PG		Total		
Time	Patient Group	Parameter	N or Median	% or Range	N or Median	% or Range	N or Median	% or Range	*P*
OP	OES	Enzyme per day (kU)	120	75–195	98	60–170	120	60–195	0.375
		Dietary therapy only	7/35	20%	11/45	24%	18/80	23%	0.637
	DM	Oral antidiabetics	15/28	54%	20/34	59%	35/62	57%	0.678
		Insulin therapy	15/28	54%	17/34	50%	32/62	52%	0.678
		Insulin units per day	18	8–43	24	6–50	19	6–50	0.625
6 mo	OES	Enzyme per day (kU)	95	25–320	78	25–320	80	25–320	0.751
		Dietary therapy only	4/38	11%	6/40	15%	10/78	13%	0.555
	DM	Oral antidiabetics	13/35	38%	12/34	35%	25/68	37%	0.801
		Insulin therapy	24/34	71%	24/34	71%	48/68	71%	1.000
		Insulin units per day	25	4–48	25	8–130	25	4–130	0.583
12 mo	OES	Enzyme per day (kU)	90	25–300	95	40–250	90	25–300	0.678
		Dietary therapy only	2/34	6%	4/35	11%	6/69	9%	0.414
	DM	Oral antidiabetics	12/32	38%	13/31	42%	25/63	40%	0.719
		Insulin therapy	23/32	72%	19/31	61%	42/63	67%	0.373
		Insulin units per day	28	2–45	22	4–64	25	2–64	0.739

P values derived from 2-sided χ^2 test and Student *t* test.
DM indicates diabetes mellitus; OES, oral enzyme supplementation; OP, operation.

decreased from 20% to 13%. The amount of enzyme units taken per day was comparable in both treatment groups.

The prevalence of diabetes mellitus rose only slightly after pancreatoduodenectomy (from 25% at operation to 31% at 12-month follow-up) and was comparable after PG and PJ. Among diabetic patients, there was an increase of insulin dependence from around 50% to around 70% after pancreatoduodenectomy, whereas the percentage of patients with dietary therapy dropped only from 23% preoperatively to 13% and 9% at 6 and 12 months, respectively. There was no significant difference between both treatment arms (Table 4).

Quality of Life and Long-term Follow-up

At the time of operation, EORTC QLQ-C30 and PAN26 scores were balanced between the treatment groups except for the physical functioning scale scores, which were higher in the PG group ($P = 0.002$). The patients assigned the lowest scores to role functioning and body image. Other major reported problems were fatigue, insomnia, pain, and digestive symptoms such as altered bowel habit. At 6 and 12 months after the operation, the most severe impairments were observed in role functioning, altered bowel habit, and fatigue. On the contrary, appetite, nausea, and hepatic symptoms improved. At 6 months, a reduced score on the financial problems scale could be observed ($P = 0.044$) in PG compared with PJ, which persisted at 12-month follow-up. Furthermore, emotional and social functioning scale scores were significantly better after PG than after PJ ($P = 0.039$ and 0.019) (see Supplemental Digital Content Table S5, available at http://links.lww.com/SLA/A782).

DISCUSSION

We report the currently largest RCT to compare PG and PJ in terms of POPF and perioperative complications and long-term outcome including quality of life. Of note, this multicenter trial was independently monitored. In contrast to previous RCTs, PG or PJ was not restricted to a specific subtype. The results of this trial have several implications for clinical practice. First, although it was designed to confirm the hypothesis of a reduction of clinically relevant POPF in patients with PG, the results show similar rates of grade B/C POPF regardless of the reconstruction method with an overall rate of 21%. This is higher than the reported range of 4% to 18% from large retrospective benchmark series (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778). The previous RCTs report fistula rates between 12% and 24% (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778). In comparison with the other RCTs, RECOPANC included the oldest patients (average 68 years vs 56–67 years in other RCTs) with the highest body mass index (average 25 vs 21–25 in other RCTs). Of note, RECOPANC is also the first RCT to report independent monitoring. Taken together, the observed POPF rate must be considered valid in view of an ageing general population with increased operative risk.

Also, overall in-hospital mortality of 6% and the 90-day mortality of 7% in this trial do not meet the usually cited 5% benchmark for pancreatoduodenectomy. It is above the reported range of 0.7% to 3.7% from current large-scale retrospective series (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778), whereas some RCTs report comparable perioperative mortality rates of 0% to 11% (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778). In agreement with a current study,[41] our data highlight the relevance of 90-day mortality figures in pancreatic surgery. It seems appropriate to accept that clinically relevant fistula rates of 20% and perioperative mortality of more than 5% mirror clinical reality even in high-volume pancreatic surgery. A similar effect was observed in the distal pancreatectomy trial, which reported a pancreatic fistula rate after distal pancreatic resection more than twice as high as previously reported in several retrospective series.[42,43]

Meta-analysis of the available RCTs[19–26] incorporating data from this trial suggests no significant reduction in POPF rates (odds ratio: 0.66; 95% confidence interval: 0.43–1.01; $P = 0.056$) (see Supplemental Digital Content Table S6, available at http://links.lww.com/SLA/A783 for details). This stands in contrast to current meta-analysis.[44]

In a multivariate analysis, the single most important factor influencing POPF rates was the quality and texture of the organ. Soft pancreatic texture, as judged intraoperatively by the surgeon, has been demonstrated to bear a higher risk for secondary complications, erosion bleeding, and mortality in previous studies.[6,9,11,24,37,38,40] It has been shown that subjective evaluation of the pancreatic hardness and texture strongly correlates with the histopathological degree of fibrosis.[40] On the one hand, pancreatic cancer and chronic pancreatitis are usually associated with hardening of the whole organ including the pancreatic remnant; on the other hand, prophylactic surgery for benign lesions such as cystic neoplasms or small tumors such as ampullary cancer is usually associated with soft pancreatic tissue.[9,19,40]

As outlined, all participating clinics were high-volume academic centers for pancreatic surgery, and there was no statistically significant center effect regarding POPF rate. Nevertheless, a high odds ratio for POPF in the low-volume surgeons indicates that besides center volume, individual surgeon volume is a relevant factor influencing complication rates in pancreatoduodenectomy.

Furthermore, from our data, it might be speculated that PG offers an easier-to-learn technique suited for less experienced surgeons, but this effect did not reach statistical significance. This opinion has also been expressed by other authors of previous RCTs[19,20,24,26] on the basis of the assumption that it is technically easier to achieve secure invagination of the pancreatic remnant with PG, especially in case of a bulky soft pancreas. Reasons given for conversion to PG instead of PJ (soft pancreas in 11 of 12 cases) in the current trial may reflect this assumption. However, operation time was not reduced with PG in the current trial, and only 2 previous RCTs[23,26] found a shorter operation time with PG.

The incidence of grade A and B postpancreatectomy hemorrhages was increased after PG. By ISGPS definition, grade A bleeding has no therapeutic consequence, but grade B events require conservative or even invasive therapy and may be sentinels of later grade C hemorrhage. The feared life-threatening (grade C) bleeding events were not increased with PG. These findings confirm previous retrospective and prospective observations, which showed increased bleeding events from PGs.[23,45,46] Meticulous hemostatic measures at the pancreatic cut surface are, therefore, advised. There was a higher rate of perioperative stroke events in patients with PGs that were not associated with the bleeding events, however. For lack of a rational explanation, this might be interpreted as an artifact of exploratory data analysis.

Our reported length of hospital stay (median, 16 days) is about twice as long as that usually reported from high-volume North American centers (see Supplemental Digital Content Table S1, available at http://links.lww.com/SLA/A778). Our explanations are that due to law-enforced universal health care insurance in Germany, patients usually do not experience financial pressure to be discharged early, and the common practice is to discharge patients home after full recovery. Even in a fast-track surgery program applied to major pancreatic resections in a German center,[47] patients were discharged at median on day 10, with a 30-day readmission rate of only 3.5%, whereas readmission rates of 15% to 20% after

pancreatoduodenectomy are currently reported from the United States.[48,49] In consequence, readmission has been highlighted as a significant problem by American scientific studies and is financially penalized in the United States but not in Germany.[47–51]

The results of long-term pancreatic function follow-up in the current trial may be interpreted as suggestive of better exocrine function in patients with PG. However, pancreatic function was not measured directly but by means of the surrogate parameters oral enzyme supplementation and steatorrhea, and the drawback of exploratory data analysis must be kept in mind. Previous RCTs with smaller case numbers have reported inconsistent outcomes.[25,26] The current study represents the largest prospective evaluation of this issue and will be followed by a prospective long-term observation of the included patients. Regarding the usually encountered opinion that pancreatic function is worse after PG compared with PJ, our results suggest that this is not the case.

Only one previous retrospective study compared quality of life after pancreatoduodenectomy with PG and PJ and found no difference, but it was unbalanced with regard to the preoperative patient status.[52] Follow-up in the present trial did not reveal differences between the treatment groups in most aspects covered by the EORTC QLQ-C30/PAN26 questionnaires. On the contrary, the few detected that differences are not large enough to be considered clinically relevant. We also interpret these as an artifact of explorative analysis of the many quality-of-life aspects. Our results, however, provide valuable data to identify major problems that impair the quality of life of patients before and after pancreatoduodenectomy: role functioning, altered bowel habit, and fatigue.

CONCLUSIONS

In summary, this trial demonstrated several salient findings. Reconstruction by PG, when not restricted to a specific subtype and evaluated in a multicenter setting, did not reduce perioperative complications. Soft pancreatic tissue quality remains the most influential factor for POPF rate. PG may offer a technically less demanding but safe anastomotic technique. However, a higher rate of postoperative grade A/B hemorrhage was observed, advocating increased awareness toward hemostatic measures with PG. The rate of POPF remains substantial and is currently underestimated. Perioperative mortality can surpass the 5% margin even in the high-volume academic pancreatic surgery setting. Both may be attributed to extended indications for pancreatoduodenectomy in an ageing population. Quality of life in pancreatoduodenectomy patients is most severely impaired regarding role functioning and body image. The operation seems to ameliorate gastrointestinal and hepatic symptoms but does not improve fatigue and role functioning. Long-term exocrine pancreatic function after PG does not seem to be inferior to PJ.

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