Systematic review

Meta-analysis of pancreaticogastrostomy *versus* pancreaticojejunostomy after pancreaticoduodenectomy

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Background: **Surgical reconstruction following pancreaticoduodenectomy (PD) is associated with significant morbidity and mortality. Because of great variability in definitions of specific complications, it remains unclear whether there is a difference in complication rates following the two commonest types of reconstruction, pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ). Published consensus definitions for postoperative pancreatic fistula (POPF) have led to a series of randomized clinical trials (RCTs) uniquely placed to address this question.**

Methods: **A literature search was carried out to identify all RCTs comparing postoperative complications of PG *versus* PJ reconstruction following PD published between January 1995 and December 2013. Pooled odds ratios (ORs) with 95 percent confidence intervals (c.i.) were calculated using fixed-effect or random-effects models.**

Results: **In total, seven RCTs with 1121 patients were included. Four of these trials applied definitions as published by the International Study Group on Pancreatic Fistula (ISGPF). Using ISGPF definitions, the incidence of POPF was lower in patients undergoing PG than in those having PJ (OR 0·50, 95 per cent c.i. 0·34 to 0·73; $P < 0·001$). Using definitions applied by each individual study, PG was associated with significantly lower rates of POPF (OR 0·51, 0·36 to 0·71; $P < 0·001$), intra-abdominal fluid collection (OR 0·50, 0·34 to 0·74; $P < 0·001$) and biliary fistula (OR 0·42, 0·18 to 0·93; $P = 0·03$) than PJ.**

Conclusion: **Meta-analysis of four RCTs based on ISGPF criteria, and seven RCTs using non-standard criteria, revealed that PG reduced the incidence of POPF after PD compared with PJ.**

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Introduction

Since the first seminal report by Whipple and colleagues[1] in 1935 of three patients who underwent pancreaticoduodenectomy (PD), it has been regarded as the standard surgical procedure for patients with either malignant or benign disease of the pancreatic head and/or periampullary region. Advances in perioperative management in recent years have helped to reduce the mortality rate associated with PD to below 5 per cent in high-volume centres[2]. The morbidity rate, however, remains stubbornly high, even greater than 50 per cent in some studies[3]. Postoperative pancreatic fistula (POPF) is the most frequent major complication of reconstruction following PD, with a reported incidence of around 2–20 per cent[4]. POPF can lead to a prolonged hospital stay and even death. There is a multitude of diverse approaches in use today aiming to reduce the incidence of POPF. Prophylactic octreotide[5], use of fibrin glue to occlude the main pancreatic duct[6], suture ligation of the pancreatic duct[7], pancreatic duct stenting[8], modification of the jejunal anastomosis (end-to-end *versus* end-to-side, invagination *versus* duct-to-mucosa)[9,10], pancreaticogastrostomy (PG)[11], use of an isolated Roux-en-Y limb to drain the pancreas[12] and total pancreatectomy[13] have all been suggested. There is, however, ongoing debate as to which is the most effective strategy.

At present, PG and pancreaticojejunostomy (PJ) are the two most widely employed techniques for the restoration of pancreatic drainage into the gastrointestinal tract after PD. PG was first described in humans by Waugh

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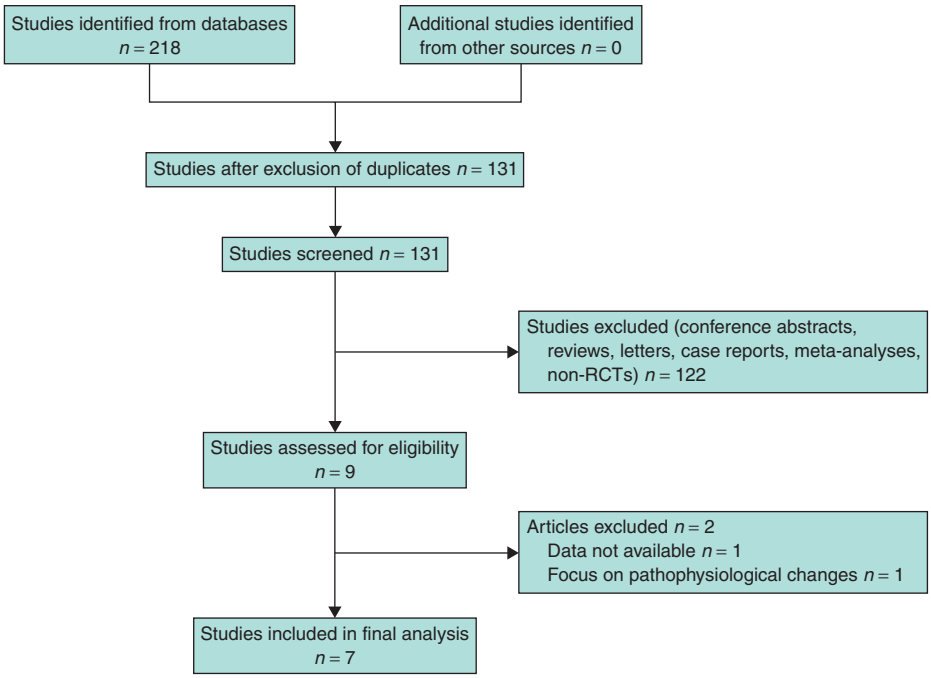


Fig. 1 PRISMA diagram showing selection of articles for review. RCT, randomized clinical trial

and Clagett in 1946[14], and has gained popularity in recent years as a result of a possible reduction in the incidence of POPF. Several non-randomized studies[5–17] demonstrated a significant reduction in POPF for PG compared with PJ[1]. In contrast, however, three randomized clinical trials (RCTs)[11,18,19] found no difference in POPF rates. Adding to the confusion, a recent meta-analysis[20] that pooled retrospective studies found a significant reduction of the POPF rate when PG was used. However, another meta-analysis[21] of four recent RCTs failed to demonstrate superiority of PG over PJ. A number of factors might explain these differences, but the most evident is the use of different definitions, before 2005, of the term 'pancreatic fistula', as well as of 'anastomotic leak' to describe similar phenomena, or indeed offering no definition at all. This particular problem has been addressed by the International Study Group on Pancreatic Fistula (ISGPF)[4] definition, published in 2005, and has resulted in subsequent publications being more comparable. Variation in operative technique and relatively low numbers in some RCTs have added further uncertainty to analyses.

Three large RCTs[22–24] using the ISGPF definitions have been published recently. Two of these[22,23] also analysed the POPF rate relating to subjectively reported pancreatic texture. Furthermore, standard definitions of other complications have recently been published by the International Study Group of Pancreatic Surgery (ISGPS)[25,26], allowing further standardization of outcome reporting.

This systematic review and meta-analysis of all RCTs published in the past 19 years included a subanalysis of trials that specifically applied the ISGPF and ISGPS definitions to clarify further the advantages and disadvantages of these two reconstruction methods.

Methods

Study selection

A comprehensive systematic literature search was carried out in MEDLINE (PubMed), Embase, Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library to identify articles relating to human trials published in the English language between January 1995 and December 2013. The following search terms were used, in all possible combinations: 'pancreaticoduodenectomy, pancreatoduodenectomy, Whipple, pancreatoduodenal resection, pancreaticojejunostomy, pancreatojejunostomy, pancreaticoenteric anastomosis, pancreaticogastrostomy, pancreatogastrostomy, and pancreaticogastric anastomosis'. A manual search of the Google Scholar database and the published abstracts from various surgical society meetings was also undertaken. The search was extended by use of the

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Table 1 Study characteristics

Reference	Country and setting	Study interval	No. of patients*	Age (years)†	Disease	Soft parenchyma (%)	Stent	Octreotide	Jadad score
Yeo *et al.*[18]	USA	1993–1995	PG 73 (33)	61·5(1·7)	BMDPP	22	No	No	4
	Single centre		PJ 72 (38)	62·4(1·4)		24	No	No	
Duffas *et al.*[19]	France	1995–1999	PG 81 (51)	58·2(11·0)	BMDPP	60	Selected	Selected	4
	Multicentre		PJ 68 (35)	58·6(12·0)		60	Selected	Selected	
Bassi *et al.*[11]	Italy	2002–2004	PG 69 (44)	(58·2–60·4)	BMDPP	100	No	All	4
	Single centre		PJ 82 (51)	(54·5–56·6)		100	No	All	
Fernández-Cruz *et al.*[33]	Spain	2005–2007	PG 53 (29)	63(13)	BMDPP	45	All	No	4
	Single centre		PJ 55 (38)	63(14)		46	All	No	
Wellner *et al.*[22]	Germany	2006–2011	PG 59 (59)	67 (34–84)	BMDPP	59	All	Selected	4
	Single centre		PJ 57 (57)	64 (23–81)	and other	51	All	Selected	
Topal *et al.*[23]	Belgium	2009–2012	PG 162 (100)	67·0 (60·6–73·5)	BMDPP	48‡	No	All	4
	Multicentre		PJ 167 (91)	66·1 (59·4–74·6)			No	All	
Figueras *et al.*[24]	Spain	2008–2012	PG 65 (44)	67 (35–80)	BMDPP	52	No	All	4
	Multicentre		PJ 58 (37)	65·5 (42–80)	and other	57	No	All	

*Values in parentheses are number of men; †values are mean(s.d.) or median (range). ‡Percentage in the two groups combined. PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; BMDPP, benign and malignant disease of the pancreatic head and periampullary region.

Table 2 Surgical technique and definition of pancreatic fistula

Reference	Operation type	PG technique	PJ technique	Definition of pancreatic fistula
Yeo *et al.*[18]	PD or PPPD	2 layers, end-to-side, PWS	2 layers, end-to-end or end-to-side	> 50 ml/day amylase-rich fluid (3× serum level) on or after POD 10, or radiographically documented leak
Duffas *et al.*[19]	PD or PPPD or extended resection	n.r.	End-to-end or end-to-side	Amylase-rich fluid (4× serum level) for 3 days, or radiographically documented
Bassi *et al.*[11]	PD or PPPD	1-layer, telescope, PWS	1 layer, side-to-side, duct-to-mucosa	Clinically significant output of fluid rich in amylase, confirmed by fistulography
Fernández-Cruz *et al.*[33]	PPPD	2 layers, end-to-side, duct-to-mucosa	End-to-side, duct-to-mucosa	ISGPF definition[4]
Wellner *et al.*[22]	PD or PPPD	Invagination, end-to-side, PWS	End-to-side, either single layer or with duct-to-mucosa	ISGPF definition[4]
Topal *et al.*[23]	PD or PPPD	End-to-side, telescoped, PWS	End-to-side, telescoped	ISGPF definition[4]
Figueras *et al.*[24]	PD or PPPD	2 layers, invaginated, PWS	2 layers, end-to-side, duct-to-mucosa	ISGPF definition[4]

PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; PWS, posterior wall of stomach; POD, postoperative day; n.r., not reported; ISGPF, International Study Group on Pancreatic Fistula.

'related article' function of databases and by scanning the references of all relevant articles. Investigators and experts in the field of pancreatic surgery were contacted to ensure that all relevant studies were identified. Final inclusion of articles was determined by consensus between the two lead authors; where this failed, a third author adjudicated.

Inclusion and exclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[27] were used as guidelines in the construction of this analysis. Studies were included based on the following criteria: English-language articles published in peer-reviewed journals; human studies; studies with at least one of the outcomes mentioned; and where multiple studies came from the same institute and/or authors, either the higher-quality study or the more recent publication was included in the analysis.

The following studies were excluded: abstracts, letters, editorials, expert opinions, case reports, reviews and studies lacking control groups; studies with inadequate description of surgical methodology or with insufficient data on outcomes; non-randomized studies; and studies that focused on pathophysiological changes.

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Table 3 Results of meta-analysis comparing pancreaticogastrostomy *versus* pancreaticojejunostomy

			Effect estimate		Heterogeneity	
Outcome of interest	No. of studies	No. of patients	Odds ratio	*P*	I^2 (%)	*P*
Non-standard fistula definition						
Pancreatic fistula	7	1121	0·51 (0·36, 0·71)	< 0·001	38	0·14
Delayed gastric emptying	6	961	0·88 (0·44, 1·72)	0·70	63	0·02
Intra-abdominal fluid collection	7	1121	0·50 (0·34, 0·74)	< 0·001	38	0·14
Biliary fistula	5	676	0·42 (0·18, 0·93)	0·03	46	0·11
Postpancreatectomy haemorrhage	6	976	1·29 (0·85, 1·96)	0·24	0	0·88
Reoperation	5	853	0·96 (0·61, 1·52)	0·87	0	0·85
Morbidity	6	1005	0·90 (0·70, 1·16)	0·41	30	0·21
Mortality	7	1121	0·82 (0·43, 1·58)	0·56	0	0·84
Studies using ISGPF definition						
Pancreatic fistula (A–C)	4	676	0·50 (0·34, 0·73)	< 0·001	0	0·49
Pancreatic fistula (B/C)	4	676	0·34 (0·21, 0·55)	< 0·001	8	0·35
Delayed gastric emptying	4	665	1·06 (0·46, 2·46)	0·89	65	0·03
Delayed gastric emptying (ISGPS B/C)	2	229	1·13 (0·58, 2·18)	0·73	49	0·16
Intra-abdominal fluid collection	4	676	0·53 (0·23, 1·25)	0·15	51	0·11
Biliary fistula	2	231	0·17 (0·03, 1·02)	0·05	0	0·64
Postpancreatectomy haemorrhage	4	676	1·45 (0·87, 2·41)	0·15	0	0·95
Postpancreatectomy haemorrhage (ISGPS B/C)	2	239	1·55 (0·61, 3·97)	0·36	0	0·83
Reoperation	3	553	1·02 (0·55, 1·89)	0·96	0	0·61
Morbidity	3	560	0·78 (0·43, 1·42)	0·42	60	0·08
Mortality	4	676	0·64 (0·26, 1·60)	0·34	0	0·83

Values in parentheses are 95 per cent confidence intervals; ISGPF, International Study Group on Pancreatic Fistula; ISGPS, International Study Group of Pancreatic Surgery.

Outcomes of interests

The primary outcome measure was the incidence of POPF. Secondary outcome measures included delayed gastric emptying, intra-abdominal fluid collection, biliary fistula, postpancreatectomy haemorrhage, reoperation, morbidity and mortality. POPF was defined in accordance with the ISGPF definition[4] or as defined by the authors in studies reported before 2006. Delayed gastric emptying was defined as the need for nasogastric decompression beyond 10 days after surgery, or using the ISGPS definition[25]. Intra-abdominal fluid collection was defined as the presence of intra-abdominal fluid on the basis of radiological evidence alone, regardless of infection and/or abscess. Biliary fistula was defined as a bilirubin-containing discharge of typical colour or determined on fistulography. Postpancreatectomy haemorrhage was defined in accordance with the ISGPS definition[26], or according to individual reports. Reoperation was defined as the need for laparotomy as a consequence of the first operation. Overall morbidity comprised all complications occurring from operation to discharge. Mortality was defined as death from any cause, before discharge from hospital.

Data collection

Data were extracted independently by two reviewers using standard forms. Judgements were made on study characteristics, quality, surgical technique and the definition of POPF, and postoperative outcomes. The RCTs were assessed according to the Jadad scoring system[28], which takes the randomization and double-blinding process into consideration, as well as a description of withdrawals or drop-outs. Study design parameters, such as sample size calculation, sequence generation, allocation concealment and definitions of outcome parameters, were also recorded.

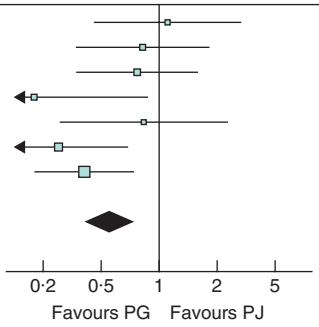
Statistical analysis

Meta-analyses were performed using Review Manager Version 5.0 software (The Cochrane Collaboration, Oxford, UK). Only categorical variables were analysed, and the treatment effects were expressed as odds ratio (OR) with corresponding 95 per cent confidence interval (c.i.). Heterogeneity was evaluated using the χ^2 test and $P < 0{\cdot}100$ was considered significant[29]. In addition,

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Reference	Pancreatic fistula PG	PJ	Weight (%)	Odds ratio (fixed)
Yeo *et al.*[18]	9 of 73	8 of 72	7·5	1·13 (0·41, 3·10)
Bassi *et al.*[11]	9 of 69	13 of 82	11·0	0·80 (0·32, 1·99)
Duffas *et al.*[19]	13 of 81	14 of 68	13·6	0·74 (0·32, 1·70)
Fernández-Cruz *et al.*[33]	2 of 53	10 of 55	10·1	0·18 (0·04, 0·85)
Wellner *et al.*[22]	6 of 59	7 of 57	6·8	0·81 (0·25, 2·57)
Figueras *et al.*[24]	7 of 65	19 of 58	19·1	0·25 (0·10, 0·65)
Topal *et al.*[23]	13 of 162	33 of 167	31·9	0·35 (0·18, 0·70)
Total	59 of 562	104 of 559	100·0	0·51 (0·36, 0·71)

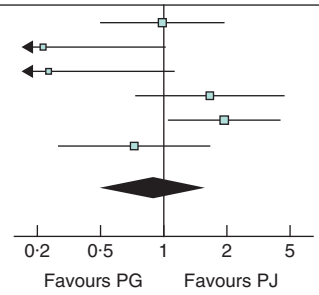
Heterogeneity: $\chi^2 = 9{\cdot}65$, 6 d.f., $P = 0{\cdot}14$; $I^2 = 38\%$
Test for overall effect: $Z = 3{\cdot}88$, $P < 0{\cdot}001$



a Pancreatic fistula

Reference	Delayed gastric emptying PG	PJ	Weight (%)	Odds ratio (random)
Yeo *et al.*[18]	16 of 73	16 of 72	20·3	0·98 (0·45, 2·15)
Bassi *et al.*[11]	2 of 69	10 of 82	11·3	0·21 (0·05, 1·02)
Fernández-Cruz *et al.*[33]	2 of 53	8 of 55	10·9	0·23 (0·05, 1·14)
Wellner *et al.*[22]	14 of 52	9 of 53	18·1	1·80 (0·70, 4·63)
Topal *et al.*[23]	25 of 162	13 of 167	21·4	2·16 (1·06, 4·39)
Figueras *et al.*[24]	9 of 65	11 of 58	17·9	0·69 (0·26, 1·80)
Total	68 of 474	67 of 487	100·0	0·88 (0·44, 1·72)

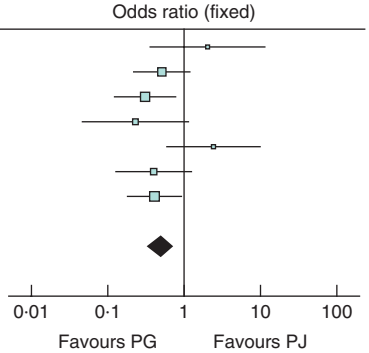
Heterogeneity: $\tau^2 = 0{\cdot}43$; $\chi^2 = 13{\cdot}52$, 5 d.f., $P = 0{\cdot}02$; $I^2 = 63\%$
Test for overall effect: $Z = 0{\cdot}39$, $P = 0{\cdot}70$



b Delayed gastric emptying

Reference	Fluid collection PG	PJ	Weight (%)	Odds ratio (fixed)
Yeo *et al.*[18]	4 of 73	2 of 72	2·6	2·03 (0·36, 11·44)
Duffas *et al.*[19]	11 of 81	16 of 68	20·2	0·51 (0·22, 1·19)
Bassi *et al.*[11]	7 of 69	22 of 82	24·2	0·31 (0·12, 0·77)
Fernández-Cruz *et al.*[33]	2 of 53	8 of 55	10·1	0·23 (0·05, 1·14)
Wellner *et al.*[22]	7 of 59	3 of 57	3·6	2·42 (0·59, 9·88)
Figueras *et al.*[24]	5 of 65	10 of 58	13·1	0·40 (0·13, 1·25)
Topal *et al.*[23]	9 of 162	21 of 167	26·2	0·41 (0·18, 0·92)
Total	45 of 562	82 of 559	100·0	0·50 (0·34, 0·74)

Heterogeneity: $\chi^2 = 9{\cdot}71$, 6 d.f., $P = 0{\cdot}14$; $I^2 = 38\%$
Test for overall effect: $Z = 3{\cdot}51$, $P < 0{\cdot}001$



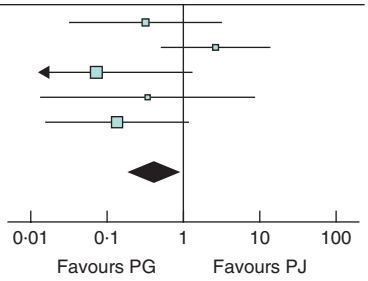
c Intra-abdominal fluid collection

Fig. 2 Forest plots illustrating results of meta-analyses comparing pancreaticogastrostomy (PG) *versus* pancreaticojejunostomy (PJ) in patients undergoing pancreaticoduodenectomy for the outcomes: **a** pancreatic fistula, **b** delayed gastric emptying, **c** intra-abdominal fluid collection, **d** biliary fistula, **e** postpancreatectomy haemorrhage, **f** reoperation, **g** morbidity and **h** mortality. Pooled odds ratios with 95 per cent confidence intervals were calculated using Mantel–Haenszel fixed-effect or random-effects models

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Reference	Biliary fistula PG	Biliary fistula PJ	Weight (%)	Odds ratio (fixed)
Yeo *et al.*[18]	1 of 73	3 of 72	15·3	0·32 (0·03, 3·15)
Duffas *et al.*[19]	6 of 81	2 of 68	10·3	2·64 (0·52, 13·53)
Bassi *et al.*[11]	0 of 69	7 of 82	34·9	0·07 (0·00, 1·29)
Fernández-Cruz *et al.*[33]	0 of 53	1 of 55	7·5	0·34 (0·01, 8·52)
Figueras *et al.*[24]	1 of 65	6 of 58	32·0	0·14 (0·02, 1·16)
Total	8 of 341	19 of 335	100·0	0·42 (0·18, 0·93)

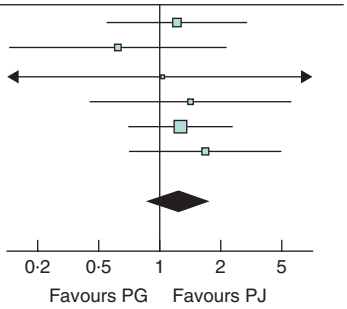
Heterogeneity: $\chi^2 = 7{\cdot}44$, 4 d.f., $P = 0{\cdot}11$; $I^2 = 46\%$
Test for overall effect: $Z = 2{\cdot}12$, $P = 0{\cdot}03$



d Biliary fistula

Reference	Haemorrhage PG	Haemorrhage PJ	Weight (%)	Odds ratio (fixed)
Duffas *et al.*[19]	13 of 81	9 of 68	21·3	1·25 (0·50, 3·14)
Bassi *et al.*[11]	3 of 69	6 of 82	13·6	0·58 (0·14, 2·39)
Fernández-Cruz *et al.*[33]	1 of 53	1 of 55	2·5	1·04 (0·06, 17·04)
Wellner *et al.*[22]	6 of 59	4 of 57	9·5	1·50 (0·40, 5·62)
Topal *et al.*[23]	21 of 162	17 of 167	37·8	1·31 (0·67, 2·59)
Figueras *et al.*[24]	13 of 65	7 of 58	15·3	1·82 (0·67, 4·93)
Total	57 of 489	44 of 487	100·0	1·29 (0·85, 1·96)

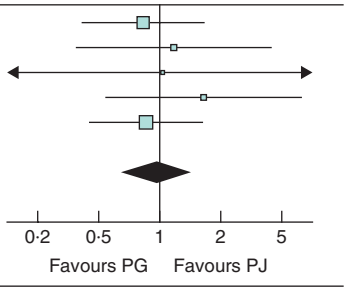
Heterogeneity: $\chi^2 = 1{\cdot}77$, 5 d.f., $P = 0{\cdot}88$; $I^2 = 0\%$
Test for overall effect: $Z = 1{\cdot}19$, $P = 0{\cdot}24$



e Postpancreatectomy haemorrhage

Reference	Reoperation PG	Reoperation PJ	Weight (%)	Odds ratio (fixed)
Duffas *et al.*[19]	15 of 81	15 of 68	35·6	0·80 (0·36, 1·79)
Bassi *et al.*[11]	5 of 69	5 of 82	11·3	1·20 (0·33, 4·34)
Fernández-Cruz *et al.*[33]	1 of 53	1 of 55	2·6	1·04 (0·06, 17·04)
Wellner *et al.*[22]	7 of 59	4 of 57	9·6	1·78 (0·49, 6·46)
Topal *et al.*[23]	14 of 162	17 of 167	40·9	0·83 (0·40, 1·75)
Total	42 of 424	42 of 429	100·0	0·96 (0·61, 1·52)

Heterogeneity: $\chi^2 = 1{\cdot}34$, 4 d.f., $P = 0{\cdot}85$; $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}17$, $P = 0{\cdot}87$



f Reoperation

Fig. 2 Continued

I^2 values were used for the evaluation of statistical heterogeneity; an I^2 value of 50 per cent or more indicated the presence of heterogeneity. A fixed-effect model was initially applied for all outcomes[30] but, if the test rejected the assumption of homogeneity of studies, a random-effects analysis was performed[31].

Subgroup analysis was undertaken based on the ISGPF definition, as well as for delayed gastric emptying and postpancreatectomy haemorrhage based on the ISGPS definitions. A funnel plot was constructed for POPF to evaluate potential publication bias[32].

Results

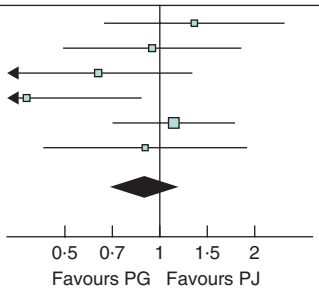
Description of randomized trials included in the meta-analysis

The initial search strategy yielded 218 articles in the database; 87 reports were excluded owing to duplication.

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Reference	Morbidity PG	Morbidity PJ	Weight (%)	Odds ratio (fixed)
Yeo *et al.*[18]	36 of 73	31 of 72	12·6	1·29 (0·67, 2·48)
Duffas *et al.*[19]	37 of 81	32 of 68	15·0	0·95 (0·50, 1·81)
Bassi *et al.*[11]	20 of 69	32 of 82	16·5	0·64 (0·32, 1·26)
Fernández-Cruz *et al.*[33]	12 of 53	24 of 55	14·5	0·38 (0·16, 0·87)
Topal *et al.*[23]	100 of 162	99 of 167	29·6	1·11 (0·71, 1·72)
Figueras *et al.*[24]	41 of 65	38 of 58	11·8	0·90 (0·43, 1·88)
Total	246 of 503	256 of 502	100·0	0·90 (0·70, 1·16)

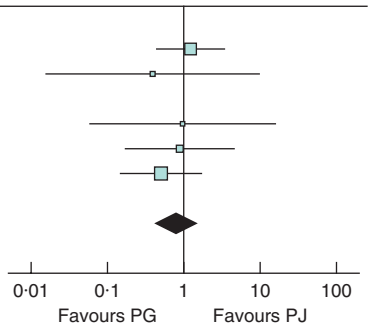
Heterogeneity: $\chi^2 = 7{\cdot}14$, 5 d.f., $P = 0{\cdot}21$; $I^2 = 30\%$
Test for overall effect: $Z = 0{\cdot}83$, $P = 0{\cdot}41$



g Morbidity

Reference	Mortality PG	Mortality PJ	Weight (%)	Odds ratio (fixed)
Yeo *et al.*[18]	0 of 73	0 of 72		Not estimable
Duffas *et al.*[19]	10 of 81	7 of 68	33·8	1·23 (0·44, 3·42)
Bassi *et al.*[11]	0 of 69	1 of 82	6·9	0·39 (0·02, 9·75)
Fernández-Cruz *et al.*[33]	0 of 53	0 of 55		Not estimable
Wellner *et al.*[22]	1 of 59	1 of 57	5·1	0·97 (0·06, 15·81)
Figueras *et al.*[24]	3 of 65	3 of 58	15·3	0·89 (0·17, 4·58)
Topal *et al.*[23]	4 of 162	8 of 167	38·9	0·50 (0·15, 1·70)
Total	18 of 562	20 of 559	100·0	0·82 (0·43, 1·58)

Heterogeneity: $\chi^2 = 1{\cdot}44$, 4 d.f., $P = 0{\cdot}84$; $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}58$, $P = 0{\cdot}56$



h Mortality

Fig. 2 Continued

Of the remaining 131 articles, 122 did not meet the set inclusion criteria and so nine full-text articles were identified for detailed investigation[11,18,19,22–24,33–35]. One report[34] was excluded because it was merely a trial protocol and did not report any data. Another study[35] was excluded as it focused on pathophysiological changes after PD, as opposed to surgical outcomes. Finally, seven studies[11,18,19,22–24,33] were included (*Fig. 1*).

Study and patient characteristics

Seven RCTs encompassing 1121 patients (562 in PG group, 559 in PJ group) were pooled for analysis. Four RCTs[11,18,22,33] were single-centre trials and three[19,23,24] were from multiple centres. All trials were conducted in Europe or North America. The sample size of each trial ranged from 108 to 329 patients. One study focused on soft pancreatic texture[11]. Three[19,22,33] reported the use of pancreatic duct stents, either internal[33] or external[22]. Octreotide was used selectively in two studies[19,22] and in all patients in three studies[11,23,24]. Both PDs and pylorus-preserving pancreaticoduodenectomies (PPPDs) were reported in five trials[11,18,22–24]. One study[19] included patients undergoing extended resections, and another[33] included only patients undergoing PPPD. Most included studies[18,22,24] used a two-layer, end-to-side, duct-to-mucosa anastomosis for the PJ. There were three main reported methods for the PG (telescoping, invagination or duct-to-mucosa anastomosis)[11,18,22–24,33]. The ISGPF definition was used in four studies[22–24,33]. Study characteristics and quality assessment scoring are summarized in *Table 1*. Surgical techniques and definition of POPF used are shown in *Table 2*.

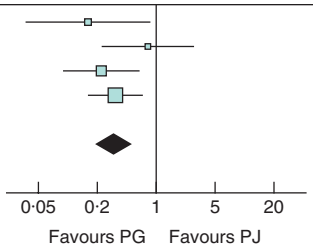
Results of the meta-analysis for all studies

All results are summarized in *Table 3* and *Fig. 2*. There was a benefit of PG compared with PJ with respect to POPF (OR 0·51, 95 per cent c.i. 0·36 to 0·71; $P < 0{\cdot}001$), biliary fistula (OR 0·42, 0·18 to 0·93; $P = 0{\cdot}03$) and intra-abdominal fluid collection (OR 0·50, 0·34 to 0·74; $P < 0{\cdot}001$). No statistically significant differences were found with respect

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Reference	Pancreatic fistula B/C		Weight (%)	Odds ratio (fixed)
	PG	PJ		
Fernández-Cruz *et al.*[33]	2 of 53	10 of 55	14·8	0·18 (0·04, 0·85)
Wellner *et al.*[22]	6 of 59	7 of 57	10·0	0·81 (0·25, 2·57)
Figueras *et al.*[24]	7 of 65	19 of 58	28·2	0·25 (0·10, 0·65)
Topal *et al.*[23]	13 of 162	33 of 167	47·0	0·35 (0·18, 0·70)
Total	28 of 339	69 of 337	100·0	0·34 (0·21, 0·55)

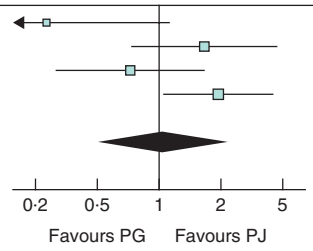
Heterogeneity: $\chi^2 = 3{\cdot}25$, 3 d.f., $P = 0{\cdot}35$; $I^2 = 8\%$
Test for overall effect: $Z = 4{\cdot}46$, $P < 0{\cdot}001$



a Pancreatic fistula

Reference	Delayed gastric emptying		Weight (%)	Odds ratio (random)
	PG	PJ		
Fernández-Cruz *et al.*[33]	2 of 53	8 of 55	16·3	0·23 (0·05, 1·14)
Wellner *et al.*[22]	14 of 52	9 of 53	26·5	1·80 (0·70, 4·63)
Figueras *et al.*[24]	9 of 65	11 of 58	26·2	0·69 (0·26, 1·80)
Topal *et al.*[23]	25 of 162	13 of 167	31·0	2·16 (1·06, 4·39)
Total	50 of 332	41 of 333	100·0	1·06 (0·46, 2·46)

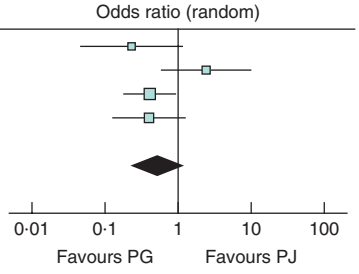
Heterogeneity: $\tau^2 = 0{\cdot}47$; $\chi^2 = 8{\cdot}65$, 3 d.f., $P = 0{\cdot}03$; $I^2 = 65\%$
Test for overall effect: $Z = 0{\cdot}13$, $P = 0{\cdot}89$



b Delayed gastric emptying

Reference	Fluid collection		Weight (%)	Odds ratio (random)
	PG	PJ		
Fernández-Cruz *et al.*[33]	2 of 53	8 of 55	18·1	0·23 (0·05, 1·14)
Wellner *et al.*[22]	7 of 59	3 of 57	21·2	2·42 (0·59, 9·88)
Topal *et al.*[23]	9 of 162	21 of 167	34·3	0·41 (0·18, 0·92)
Figueras *et al.*[24]	5 of 65	10 of 58	26·4	0·40 (0·13, 1·25)
Total	23 of 339	42 of 337	100·0	0·53 (0·23, 1·25)

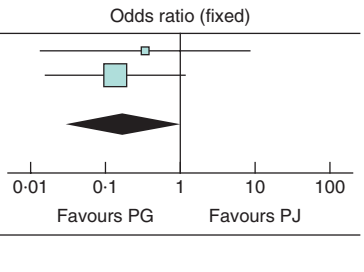
Heterogeneity: $\tau^2 = 0{\cdot}38$; $\chi^2 = 6{\cdot}13$, 3 d.f., $P = 0{\cdot}11$; $I^2 = 51\%$
Test for overall effect: $Z = 1{\cdot}44$, $P = 0{\cdot}15$



c Intra-abdominal fluid collection

Reference	Biliary fistula		Weight (%)	Odds ratio (fixed)
	PG	PJ		
Fernández-Cruz *et al.*[33]	0 of 53	1 of 55	18·9	0·34 (0·01, 8·52)
Figueras *et al.*[24]	1 of 65	6 of 58	81·1	0·14 (0·02, 1·16)
Total	1 of 118	7 of 113	100·0	0·17 (0·03, 1·02)

Heterogeneity: $\chi^2 = 0{\cdot}22$, 1 d.f., $P = 0{\cdot}64$; $I^2 = 0\%$
Test for overall effect: $Z = 1{\cdot}94$, $P = 0{\cdot}05$



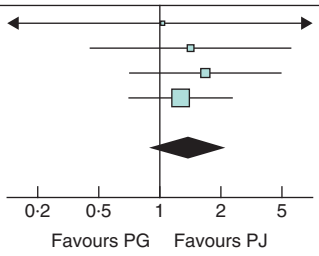
d Biliary fistula

Fig. 3 Forest plots illustrating results of meta-analyses comparing pancreaticogastrostomy (PG) *versus* pancreaticojejunostomy (PJ) in patients undergoing pancreaticoduodenectomy, from studies using the International Study Group on Pancreatic Fistula definition, for the outcomes: **a** pancreatic fistula B/C, **b** delayed gastric emptying, **c** intra-abdominal fluid collection, **d** biliary fistula, **e** post-pancreatectomy haemorrhage, **f** reoperation, **g** morbidity and **h** mortality. Pooled odds ratios with 95 per cent confidence intervals were calculated using Mantel–Haenszel fixed-effect or random-effects models

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Reference	Haemorrhage PG	Haemorrhage PJ	Weight (%)	Odds ratio (fixed)
Fernández-Cruz *et al.*[33]	1 of 53	1 of 55	3·8	1·04 (0·06, 17·04)
Wellner *et al.*[22]	6 of 59	4 of 57	14·6	1·50 (0·40, 5·62)
Figueras *et al.*[24]	13 of 65	7 of 58	23·6	1·82 (0·67, 4·93)
Topal *et al.*[23]	21 of 162	17 of 167	58·0	1·31 (0·67, 2·59)
Total	41 of 339	29 of 337	100·0	1·45 (0·87, 2·41)

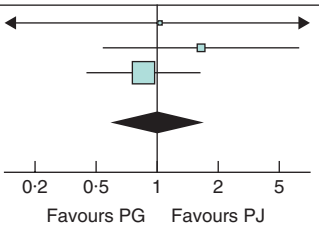
Heterogeneity: $\chi^2 = 0{\cdot}34$, 3 d.f., $P = 0{\cdot}95$; $I^2 = 0\%$
Test for overall effect: $Z = 1{\cdot}44$, $P = 0{\cdot}15$



e Postpancreatectomy haemorrhage

Reference	Reoperation PG	Reoperation PJ	Weight (%)	Odds ratio (fixed)
Fernández-Cruz *et al.*[33]	1 of 53	1 of 55	4·9	1·04 (0·06, 17·04)
Wellner *et al.*[22]	7 of 59	4 of 57	18·1	1·78 (0·49, 6·46)
Topal *et al.*[23]	14 of 162	17 of 167	77·1	0·83 (0·40, 1·75)
Total	22 of 274	22 of 279	100·0	1·02 (0.55, 1·89)

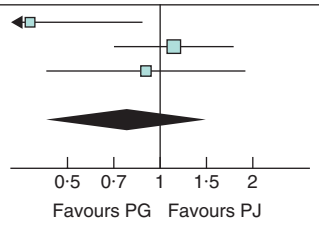
Heterogeneity: $\chi^2 = 1{\cdot}00$, 2 d.f., $P = 0{\cdot}61$; $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}05$, $P = 0{\cdot}96$



f Reoperation

Reference	Morbidity PG	Morbidity PJ	Weight (%)	Odds ratio (random)
Fernández-Cruz *et al.*[33]	12 of 53	24 of 55	26·9	0·38 (0·16, 0·87)
Topal *et al.*[23]	100 of 162	99 of 167	42·9	1·11 (0·71, 1·72)
Figueras *et al.*[24]	41 of 65	38 of 58	30·3	0·90 (0·43, 1·88)
Total	153 of 280	161 of 280	100·0	0·78 (0·43, 1·42)

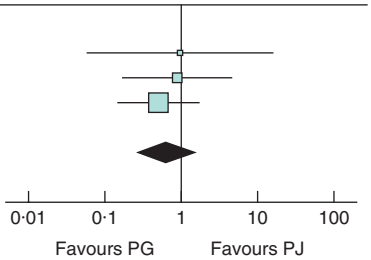
Heterogeneity: $\tau^2 = 0{\cdot}17$; $\chi^2 = 4{\cdot}98$, 2 d.f., $P = 0{\cdot}08$; $I^2 = 60\%$
Test for overall effect: $Z = 0{\cdot}81$, $P = 0{\cdot}42$



g Morbidity

Reference	Mortality PG	Mortality PJ	Weight (%)	Odds ratio (fixed)
Fernández-Cruz *et al.*[33]	0 of 53	0 of 55		Not estimable
Wellner *et al.*[22]	1 of 59	1 of 57	8·5	0·97 (0·06, 15·81)
Figueras *et al.*[24]	3 of 65	3 of 58	25·8	0·89 (0·17, 4·58)
Topal *et al.*[23]	4 of 162	8 of 167	65·6	0·50 (0·15, 1·70)
Total	8 of 339	12 of 337	100·0	0·64 (0·26, 1·60)

Heterogeneity: $\chi^2 = 0{\cdot}38$, 2 d.f., $P = 0{\cdot}83$; $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}95$, $P = 0{\cdot}34$



h Mortality

Fig. 3 Continued

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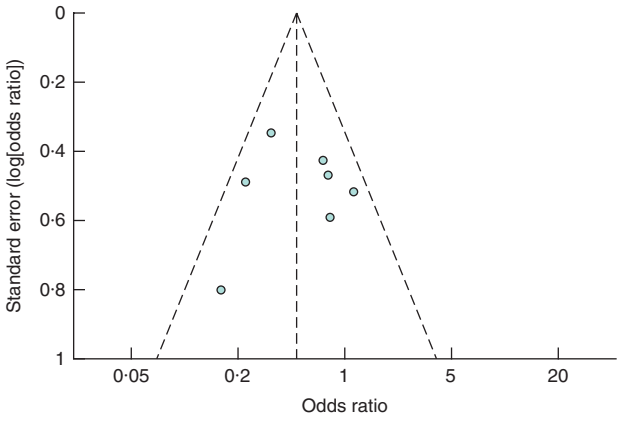


Fig. 4 Funnel plot to investigate publication bias, based on pancreatic fistula, in all included studies. The funnel plot revealed no publication bias

to delayed gastric emptying (OR 0·88, 0·44 to 1·72; $P = 0·70$), postpancreatectomy haemorrhage (OR 1·29, 0·85 to 1·96; $P = 0·24$), reoperation rates (OR 0·96, 0·61 to 1·52; $P = 0·87$), morbidity (OR 0·90, 0·70 to 1·16; $P = 0·41$) or mortality (OR 0·82, 0·43 to 1·58; $P = 0·56$).

Subgroup analyses

Results of the subgroup analysis are shown in *Table 3* and *Fig. 3*. When studies using the ISGPF definition were pooled (4 studies, 676 patients), patients undergoing PG reconstruction still had lower rates of POPF than those having PJ reconstruction (OR 0·50, 0·34 to 0·73; $P < 0·001$). However, there were no statistically significant differences in any other outcome. Moreover, this difference persisted and indeed was more pronounced when only the most severe cases of POPF were considered (ISGPF grades B and C) (OR 0·34, 0·21 to 0·55; $P < 0·001$). There were no statistically significant differences between the groups based on the ISGPS B and C grades for delayed gastric emptying (OR 1·13, 0·58 to 2·18; $P = 0·73$) or postpancreatectomy haemorrhage (OR 1·55, 0·61 to 3·97; $P = 0·36$). Importantly, patients a with soft pancreas undergoing PG reconstruction had lower rates of POPF than those having PJ reconstruction (OR 0·50, 0·29 to 0·85; $P = 0·01$).

Publication bias

There was no evidence of publication bias as determined from a funnel plot based on POPF (*Fig. 4*).

Discussion

This meta-analysis of seven RCTs revealed a significant benefit of PG reconstruction compared with PJ reconstruction with regard to POPF, intra-abdominal fluid collection and biliary fistula. Subgroup analysis looking specifically at trials using the ISGPF definition also favoured PG reconstruction. This study advances understanding of the complication profile of PG *versus* PJ following PD. It is worth noting that a previous meta-analysis[21] which failed to demonstrate a statistically significant difference in POPF rates did tend to favour PG over PJ (RR 0·73, 0·48 to 1·10). The present analysis, however, included four well conducted large trials using clear and consistent definitions of outcomes and, based on these data, PG can be recommended over PJ for pancreatic reconstruction with following PD owing to its relatively lower rate of major complications. However, there was no statistically significant difference in overall morbidity between the two groups, which may be attributed to the different definitions of included complications.

There are a number of plausible explanations for why PG may be superior to PJ reconstruction in reducing the POPF rate. First, deleterious tissue digestion around the PG site may be prevented because pancreatic enzymes are not activated by the gastric acidic environment[36] and a lack of enterokinase[37] in the gastric lumen. Second, the rich blood supply to the stomach wall promotes PG healing and the larger area of stomach wall makes invagination of the pancreatic stump into the stomach technically easier, especially when the pancreatic stump is bulky. Finally, the stomach may be decompressed by means of a nasogastric tube and accessed easily using an endoscope to assess the situation of the pancreatic stump following PG, potentially avoiding unnecessary re-explorations[38,39]. PJ is technically more demanding than PG. A surgeon's learning curve and the centre's case volume can influence the choice of anastomosis and risk of postoperative complications, especially POPF.

The present analysis found no significant difference in rates of delayed gastric emptying between the two groups. Major reported risk factors for delayed gastric emptying include intra-abdominal abscess, anastomotic leakage[40,41] and resection technique (standard Whipple procedure *versus* PPPD)[42,43]. Moreover, old age and early enteral nutrition have also been identified as independent risk factors for delayed gastric emptying[44]. The incidence of POPF was significantly higher in the PJ than in the PG group, which should have been reflected in a higher rate of delayed gastric emptying in the PJ group. However, in the present study, there was no statistically significant difference in delayed gastric emptying between the two groups. The large variation in reporting and diagnostic criteria may be the primary reason for this. Another contributing factor could be the actual PG technique used. Pyloric resection

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and posterior gastrotomy for pancreas implantation *versus* posterior and anterior gastrotomy for PG reconstruction in PPPD[45] could conceivably account for differences in resulting gastroparesis and pylorospasm secondary to gastric denervation[17].

Early or delayed haemorrhage can occur from a number of sites after PD, including the hepaticojejunostomy, pancreatic anastomosis or non-anastomotic lesions. Extraluminal bleeding is generally associated with the development of a POPF[22]. However, this variable was not examined specifically in the present analysis because only two studies[22,24] reported extraluminal and intraluminal bleeding. One study[22] found no significant difference in these two types of postpancreatectomy haemorrhage; the other[24] suggested that early intraluminal bleeding was more frequent in the PG group, whereas late extraluminal bleeding secondary to POPF was more common in the PJ group (3 of 7 patients) and early extraluminal bleeding was similar in the two groups (6 of 13 for PG *versus* 4 of 7 for PJ). One report[46] suggested that PJ was associated with a higher rate of postpancreatectomy haemorrhage as a result of erosion of adjacent tissue by activated pancreatic enzymes and a high volume of pancreatic juice. The absence of a statistically significant difference in postpancreatectomy haemorrhage rates between the two groups here can be explained by lack of sufficient data for separate analysis of extraluminal and intraluminal bleeding.

Similarly, there was no statistically significant difference in intra-abdominal fluid collection (including intraperitoneal abscess) when the ISGPS definition was used. In the analysis including all studies, however, PG was associated with significantly lower rates of intra-abdominal fluid collection. This may be because the POPF rate was lower in the PG group than in the PJ group. Furthermore, the risk of biliary fistula was similarly lower following PG reconstruction, which may be related to the nearby double anastomosis in PJ reconstruction (pancreatojejunal and hepaticodochojejunal); this could conceivably add an element of tension resulting from the afferent jejunal loop being fixed in two places in close proximity.

The limitations of this meta-analysis should be recognized. First, there was clinical heterogeneity in some outcomes, such as delayed gastric emptying, intra-abdominal fluid collection and morbidity. This was due to the differences in operative technique (PD *versus* PPPD, duct-to-mucosa *versus* invagination of stump, end-to-end *versus* end-to-side anastomoses, use of octreotide, use of pancreatic stents) as well as in the consistency of pancreatic parenchyma (hard *versus* soft), Second, owing to lack of detailed information in the included studies, it was not possible to perform a subgroup analysis based on surgical technique and pancreatic duct diameter. Third, there were insufficient data for a pooled analysis of endocrine or exocrine function after PG or PJ; only one of the included RCTs[24] reported equal endocrine and superior exocrine function in the PG reconstruction group. However, in one non-randomized study[47] of PG after PD, with a median follow-up of 3 years, patients remained free from diabetes but developed marked pancreatic exocrine insufficiency. Another non-randomized trial[48] suggested that preservation of pancreatic exocrine function was better after PJ. This may be explained by the fact that pancreatic amylase and lipase are inactivated at low pH (less than 3·0) following PG[47]. Besides the effect of parenchymal reduction, POPF might further compromise exocrine function by causing stricturing of the pancreatic anastomosis[49]. Because of this uncertainty, it is important that future RCTs clearly document long-term outcomes following PG or PJ.

This analysis has demonstrated that PG reconstruction following PD is as safe as PJ reconstruction, and may be superior with respect to its most serious complication, POPF. However, there is a need for well designed RCTs with long-term follow-up comparing PG and PJ reconstruction with respect to other complications and overall morbidity, and in more selective situations such as PPPD *versus* PD.

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