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META-ANALYSIS

Meta-analysis of subtotal stomach-preserving pancreaticoduodenectomy *vs* pylorus preserving pancreaticoduodenectomy

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Abstract

AIM: To investigate the differences in outcome following pylorus preserving pancreaticoduodenectomy (PPPD) and subtotal stomach-preserving pancreaticoduodenectomy (SSPPD).

METHODS: Major databases including PubMed (Medline), EMBASE and Science Citation Index Expanded and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched for comparative studies between patients with PPPD and SSPPD published between January 1978 and July 2014. Studies were selected based on specific inclusion and exclusion criteria. The primary outcome was delayed gastric emptying (DGE). Secondary outcomes included operation time, intraoperative blood loss, pancreatic fistula, postoperative hemorrhage, intraabdominal abscess, wound infection, time to starting liquid diet, time to starting solid diet, period of nasogastric intubation, reinsertion of nasogastric tube, mortality and hospital stay. The pooled odds ratios (OR) or weighted mean difference (WMD) with 95% confidence intervals (95%CI) were calculated using either a fixed-effects or random-effects model.

RESULTS: Eight comparative studies recruiting 650 patients were analyzed, which include two RCTs, one non-randomized prospective and 5 retrospective trial designs. Patients undergoing SSPPD experienced significantly lower rates of DGE (OR = 2.75; 95%CI: 1.75-4.30, $P < 0.00001$) and a shorter period of nasogastric intubation (OR = 2.68; 95%CI: 0.77-4.58,

P < 0.00001), with a tendency towards shorter time to liquid (WMD = 2.97, 95%CI: -0.46-7.83; P = 0.09) and solid diets (WMD = 3.69, 95%CI: -0.46-7.83; P = 0.08) as well as shorter inpatient stay (WMD = 3.92, 95%CI: -0.37-8.22; P = 0.07), although these latter three did not reach statistical significance. PPPD, however, was associated with less intraoperative blood loss than SSPPD [WMD = -217.70, 95%CI: -429.77-(-5.63); P = 0.04]. There were no differences in other parameters between the two approaches, including operative time (WMD = -5.30, 95%CI: -43.44-32.84; P = 0.79), pancreatic fistula (OR = 0.91; 95%CI: 0.56-1.49; P = 0.70), postoperative hemorrhage (OR = 0.51; 95%CI: 0.15-1.74; P = 0.29), intraabdominal abscess (OR = 1.05; 95%CI: 0.54-2.05; P = 0.89), wound infection (OR = 0.88; 95%CI: 0.39-1.97; P = 0.75), reinsertion of nasogastric tube (OR = 1.90; 95%CI: 0.91-3.97; P = 0.09) and mortality (OR = 0.31; 95%CI: 0.05-2.01; P = 0.22).

CONCLUSION: SSPPD may improve intraoperative and short-term postoperative outcomes compared to PPPD, especially DGE. However, these findings need to be further ascertained by well-designed randomized controlled trials.

Key words: Pancreaticoduodenectomy; Pylorus preserving Subtotal stomach preserving pancreaticoduodenectomy; Delayed gastric emptying; Pancreatic surgery; Meta-analysis

Core tip: As far as we know, pancreatoduodenectomy is one of the most complicated gastrointestinal operations and is associated with a number of serious postoperative complications. Modifications of standard operating techniques aim to reduce the incidence of complications and improve quality of life of patients while maintaining oncological effectiveness. Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) was specifically designed to reduce the incidence of delayed gastric emptying (DGE) and thus shorten recovery time in patients with pancreatic head and periampullary tumors. This study clarified that, compared to pylorus preserving pancreaticoduodenectomy (PPPD), SSPPD has a lower rate of DGE, shorter operation time and a shorter period of nasogastric intubation, albeit with no significant difference in pancreatic fistula and other postoperative complications. Therefore, SSPPD can improve intraoperative and short-term postoperative outcomes compared to PPPD for patients with pancreatic head and periampullary lesions.

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INTRODUCTION

In 1935, Whipple introduced a two-stage pancreaticoduodenectomy for patients with carcinoma of the ampulla of Vater[1]. In 1941, he reported a one-stage pancreaticoduodenectomy with resection of distal stomach and duodenum[2]. Soon afterwards, the first pylorus preserving pancreaticoduodenectomy (PPPD) was performed by Watson[3] in 1944. PPPD was also used by Traverso and Longmire[4] to preserve gastrointestinal function in 1978 and since then this procedure has been extensively applied to patients with tumors of the pancreatic head as well as periampullary malignancies.

Classic Whipple's and PPPD are now considered to be the most widely employed surgical procedures for the treatment of pancreatic head and periampullary tumors[5-8]. Whereas a classic Whipple's procedure includes resection of the pancreatic head, duodenum, gallbladder, distal common bile duct, partial jejunum and distal stomach, in a PPPD the proximal duodenum is transected 3 to 4 cm distal to the pylorus ring. While some randomized controlled trials (RCTs) and meta-analyses suggest that these two procedures are comparable in terms of postoperative complications, long-term survival rates and quality of life[6-9], other studies have reported that PPPD is superior to pancreaticoduodenectomy with antrectomy as it results in a reduced occurrence of dumping, diarrhea and bile reflux gastritis, thereby possibly affording patients with an improved nutritional status[10-12].

Delayed gastric emptying (DGE) is regarded as one of the most common postoperative complications of PPPD. This can potentially prolong the hospital stay, affecting patient quality of life and increasing hospital costs[12-16]. Decreasing the occurrence of DGE, therefore, is of particular importance in patients undergoing any type of pancreaticoduodenectomy. Subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) was initially described during the 1990s in Japan. This procedure was intended to preserve the pooling ability of the stomach and minimize the occurrence of DGE[17,18]. It involves division of the stomach 2-3 cm proximal to the pylorus ring with resection of the entire duodenum distal to the site of transection, thereby removing the pylorus but retaining much of the body of the stomach compared to a classical Whipple's procedure. The rate of postoperative DGE after pancreaticoduodenectomy is controversial and whether SSPPD is able to reduce it and other postoperative complications compared to PPPD remains to be elucidated[19]. We, therefore, carried out a systematic review of the literature to investigate this issue.

MATERIALS AND METHODS

Study selection

Major databases like PubMed (Medline), EMBASE and Science Citation Index Expanded and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched for studies comparing SSPPD with PPPD from January 1978 to July 2014. The following medical search headings (MeSH) were used: "pancreaticoduodenectomy", "pancreatoduodenectomy", "Whipple", "pancreatoduodenal resection", "pylorus preserving pancreaticoduodenectomy", "PPPD", "subtotal stomach preserving pancreaticoduodenectomy", "SSPPD", "delayed gastric emptying" "pancreatic surgery", "comparative study" and combinations of them were used for word searches. References cited in the selected articles were also assessed to identify relevant studies in case studies were missed during the initial database searches. If needed, 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 of two researchers; when this failed, a third author adjudicated.

Inclusion and exclusion criteria

Two authors scrutinized potentially eligible studies using the following inclusion criteria: (1) English language full-text articles published in peer-reviewed journals; (2) human clinical trials comparing "PPPD" and "SSPPD"; (3) studies where DGE was mentioned; and (4) where multiple studies came from the same institute and/or authors using the same patient cohorts, the higher quality study was included in the analysis.

Studies were excluded if any of the following conditions existed: (1) abstracts, case reports, letters, editorials, expert opinions and reviews; (2) primary postoperative outcome unavailable; and (3) studies focused on long-term outcomes.

Outcomes of interest

DGE was the primary outcome of interest. Secondary outcomes including operation time, intraoperative blood loss, pancreatic fistula, postoperative hemorrhage, intraabdominal abscess, wound infection, time to starting liquid diet, time to starting solid diet, period of nasogastric intubation, reinsertion of nasogastric tube, mortality and hospital stay were also compared.

Data extraction and quality assessment

Data were collected by two independent researchers using standardized proformas and included: Study characteristics, surgical reconstructions, definition of DGE and postoperative management. Means of the outcomes were used for meta-analysis if not otherwise mentioned. If medians were used in some studies instead of means, the means were estimated using the following formula: (low end of range + median*2 + high end of range)/4 for a sample size smaller than 25. For a sample size greater than 25, means were estimated as the medians. When only a range was given, the standard deviations were estimated as range/4[20].

The qualitative assessment of the RCTs was based on the Jadad scoring system[21] which took into consideration the randomization and double blinding process and the description of withdrawals or dropouts. Note was also made of sample size calculation, sequence generation, allocation concealment and the definitions of outcome parameters. The non-randomized trials were assessed on the basis of the method described by McKay *et al*[22] which included assessment of the following parameters: prospective *vs* retrospective data collection; assignment to the PPPD group or the SSPPD group by means other than the surgeon's preference; and an explicit definition of DGE (studies were given a score of 1 for each of these areas; score 1-4).

Statistical analysis

Meta-analysis was performed using Review Manager Version 5.0 software (The Cochrane Collaboration, Oxford, United Kingdom). Continuous variables and categorical variables were expressed as weighted mean difference (WMD) and odds ratio (OR) with their respective corresponding 95% confidence interval (CI). Chi-square test was used to assess heterogeneity and a $P < 0.1$ was considered significant. I^2 values were used for the evaluation of statistical heterogeneity: an I^2 value of 50% or more was indicative of presence of heterogeneity[23]. The fixed-effects model was initially used for all outcomes[24], while the random-effects model was used if the test rejected the assumption of homogeneity of studies[25]. Descriptive methods were also used if the data were considered to be inappropriate for meta-analysis. Sensitivity analyses were performed by removing individual studies from the data set and analyzing the effect on the overall results, identifying sources of significant heterogeneity. Subgroup analyses were undertaken by including studies with the International Study Group of Pancreatic Surgery (ISGPS) definitions, reconstruction with pancreaticojejunostomy or pancreaticogastrostomy, RCTs or non-RCTs, and D1 or D2 lymph node dissection. Funnel plots[26] were constructed to evaluate potential publication bias based on the primary outcome - DGE.

RESULTS

Description of included trials in the meta-analysis

The search strategy initially identified 148 relevant

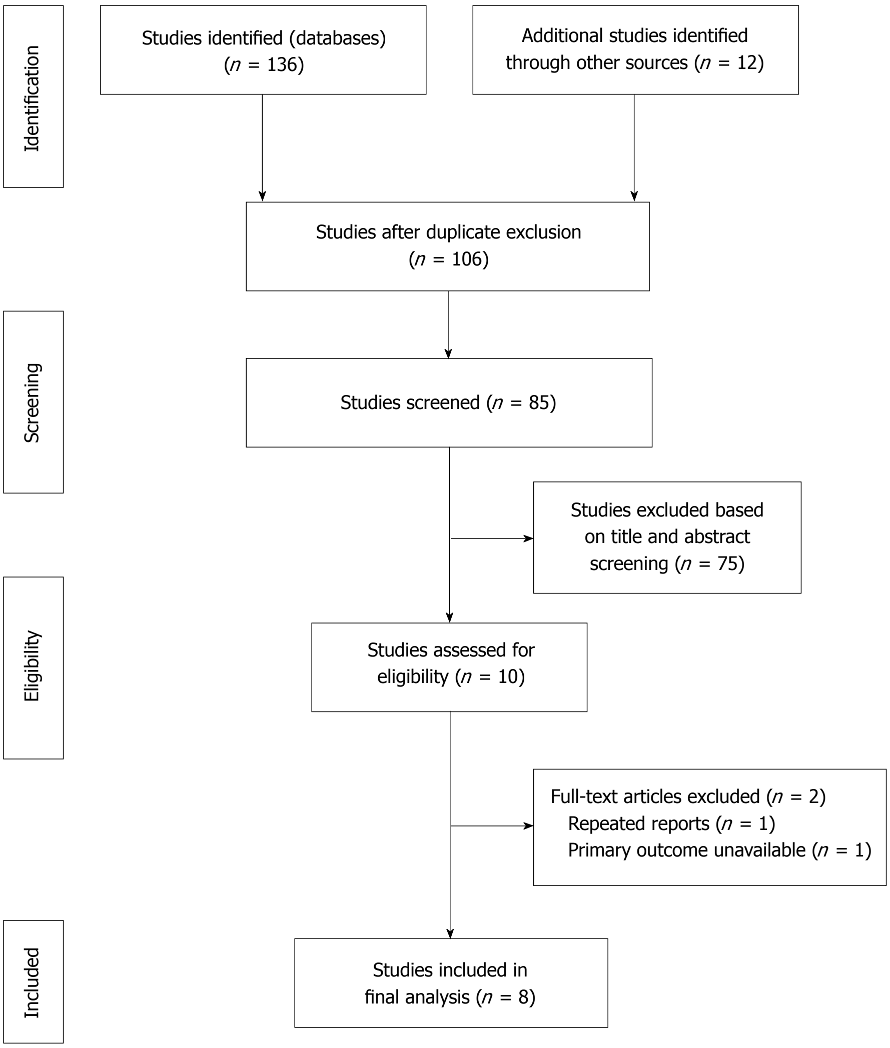


Figure 1 Flow diagram depicting the study selection process in accordance with PRISMA guidelines.

clinical trials. After filtering the studies using the inclusion criteria, ten studies[17,27-35] with full-text were identified to investigate the details. Of these, two studies[32,34] were excluded: one study[34] focused on the long-time outcomes of the same cohorts reported by their previous study; another study[32] had no data available. Finally, eight studies were identified for inclusion: two RCTs[29,35], one prospective non-randomized trials[27] and five retrospective studies[17,28,30,31,33]. Pancreaticojejunostomy was used in 6 studies[17,27,29,31,33,35], while pancreaticogastrostomy was used in two studies[28,30]. A total of 650 patients were included: 294 and 356 patients in the PPPD and SSPPD groups respectively. The ISGPS definition of DGE was used in six studies[28-31,33,35]. Indications for removal of nasogastric tube were reported in six studies[27-29,31,33,35]. All the included studies were from Japan. Figure 1 shows the process of selecting comparative studies included in our meta-analysis. The study characteristics and quality assessments are shown in Table 1. The surgical reconstruction, definition of DGE and postoperative management are listed in Table 2.

Results of meta-analysis

Results of the analyses are shown in Figures 2 and 3 and summarized in Table 3.

All included studies reported the occurrence rate of DGE. Patients in the SSPPD group had a lower incidence of DGE compared to those in the PPPD group (OR = 2.75, 95%CI: 1.75-4.30; P < 0.00001) and the period of nasogastric intubation was also shorter in the SSPPD group (WMD = 2.68, 95%CI: 0.77-4.58; P = 0.006). Furthermore, there was a tendency towards shorter time to liquid (WMD = 2.97, 95%CI: -0.46-7.83; P = 0.09) and solid diets (WMD = 3.69, 95%CI: -0.46-7.83; P = 0.08) as well as shorter hospital stay (WMD = 3.92, 95%CI: -0.37-8.22; P = 0.07), although the latter three did not reach statistical significance. PPPD was, however, associated with less intraoperative blood loss compared to SSPPD (WMD = -217.70, 95%CI: -429.77-(-5.63); P = 0.04). There were no differences in operating time (WMD = -5.30, 95%CI: -43.44-32.84; P = 0.79) or outcomes such as pancreatic fistula (OR = 0.91; 95%CI: 0.56-1.49; P = 0.70), postoperative hemorrhage (OR = 0.51; 95%CI: 0.15-1.74; P = 0.29), intraabdominal abscess (OR =

Table 1 Characteristics of the included studies

Ref.	Country	Year	Design	Group	*n*	Sex (M/F)	Age[1]	Benign/ malignant	Quality score
Hayashibe *et al*[17]	Japan	2007	Retro	PPPD	12	4/8	60.9 ± 8.5	0/12	1 (McKay)
				SSPPD	21	8/13	64.3 ± 9.5	1/20	
Akizuki *et al*[27]	Japan	2008	PNR	PPPD	34	20/14 18/12	66 (28-78)	15/19	2 (McKay)
				SSPPD	30		65 (39-79)	4/26	
Kurahara *et al*[28]	Japan	2010	Retro	PPPD	48	26/22 38/26	64.4	18/30	1 (McKay)
				SSPPD	64		66.8	11/53	
Oida *et al*[30]	Japan	2011	Retro	PPPD	25	21/4	66.2 ± 4.7	0/25	1 (McKay)
				SSPPD	42	30/12	65.8 ± 5.8	0/42	
Kawai *et al*[29]	Japan	2011	RCT	PPPD	64	33/31 38/28	68 ± 9	12/52	3 (Jadad)
				SSPPD	66		67 ± 9	14/52	
Fujii *et al*[31]	Japan	2012	Retro	PPPD	33	19/14	63.8 (35-83)	0/33	1 (McKay)
				SSPPD	56	28/28	64.6 (41-84)	0/56	
Nanashima *et al*[33]	Japan	2013	Retro	PPPD	28	21/7	68 ± 8	7/21	1 (McKay)
				SSPPD	27	15/12	66 ± 12	5/22	
Matsumoto *et al*[35]	Japan	2014	RCT	PPPD	50	29/21 35/15	66 ± 10	18/32	3 (Jadad)
				SSPPD	50		67 ± 9	21/29	

[1]Mean ± SD, standard deviation or Median and range. Retro: Retrospective observational study; PNR: Prospective nonrandomized observational study; RCT: Randomized controlled trial; SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy.

Table 2 Surgical reconstruction, definition of delayed gastric emptying and postoperative management

Ref.	Reconstruction	Definition of DGE	Indication for removing NGT	PPI	PA
Hayashibe *et al*[17]	Duct to mucosa and end-to-side pancreaticojejunostomy, end-to-side antecolic gastrojejunostomy, and side-to-side jejunojejunostomy (Braun anastomosis)	(1) NGT ≥ POD 10 (2) inability to tolerate a solid diet ≥ POD 14	Unknown	Unknown	Unknown
Akizuki *et al*[27]	Duct-to-mucosa and end-to-side pancreaticojejunostomy, end duodenal (or stomach)-to-side jejunal, Braun anastomosis was made	(1) NGT ≥ POD 10 (2) inability to tolerate a solid diet ≥ POD 14	The fluid of NGT < 500 mL per night, generally removed on POD 1	Yes	Yes
Kurahara *et al*[28]	End-to-side pancreaticogastrostomy with an internal stent, end-to-side duodenojejunostomy (PPPD) or gastrojejunostomy (SSPPD)	ISGPS	The fluid of NGT < 500 mL per night	Yes	Yes
Oida *et al*[30]	Pancreaticogastrostomy and end to end duodenojejunostomy (PPPD) Pancreaticogastrostomy and end to end gastrojejunostomy (SSPPD)	ISGPS	Unknown	Unknown	Unknown
Kawai *et al*[29]	Duct-to-mucosa, end-to-side pancreatojejunostomy with internal stent Duodenojejunostomy (PPPD), gastrojejunostomy (SSPPD)	ISGPS	All removed on POD 1	No	No
Fujii *et al*[31]	End-to-side pancreaticojejunostomy and end-to-side antecolic gastrojejunostomy in SSPPD or a duodenojejunostomy in PPPD	ISGPS	Generally removed on POD 1, or on POD 2 if the fluid of NGT > 500 mL per night	Unknown	Unknown
Nanashima *et al*[33]	End-to-side with external stent pancreatojejunostomy	ISGPS	The fluid of the NGT < 300 mL per night	Yes	Unknown
Matsumoto *et al*[35]	End-to-side pancreatojejunostomy, end-to-side duodenojejunostomy (PPPD) and gastrojejunstomy (SSPPD)	ISGPS	The fluid of the NGT < 200 mL per night	Yes	Unknown

ISGPS: International Study Group on Pancreatic Surgery; SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; POD: Postoperative day; DGE: Delayed gastric emptying; NGT: Nasogastric tube; SSA: Somatostatin analogues; PPI: Proton pump inhibitors; PA: Prokinetic agents.

1.05; 95%CI: 0.54-2.05; P = 0.89), wound infection (OR = 0.88; 95%CI: 0.39-1.97; P = 0.75), reinsertion of nasogastric tube (OR = 1.90; 95%CI: 0.91-3.97; P = 0.09), mortality (OR = 0.31; 95%CI: 0.05-2.01; P = 0.22) and hospital stay.

Sensitivity and subgroup analysis

Sensitivity analyses were carried out by excluding each study out of each outcome measure. These exclusions did not alter the results obtained from cumulative analyses. The subgroup analyses were undertaken for all outcome measures by including studies with ISGPS definition or other definition, studies with pancreaticogastrostomy or pancreaticojejunostomy, RCTs or non-randomized trials, and D1 or D2 lymph node dissection. Results of the analyses are also

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Hayashibe 2007	6	12	3	21	4.5%	6.00 (1.13, 31.73)	2007
Akizuki 2008	3	34	3	30	12.1%	0.87 (0.16, 4.68)	2008
Kurahara 2010	31	48	35	64	44.1%	1.51 (0.70, 3.26)	2010
Kawai 2011	11	64	3	66	10.2%	4.36 (1.16, 16.44)	2011
Oida 2011	25	25	42	42		Not estimable	2011
Fujii 2012	9	33	3	56	6.7%	6.63 (1.65, 26.67)	2012
Nanashima 2013	27	28	16	27	2.4%	18.56 (2.19, 157.53)	2013
Matsumoto 2014	10	50	6	50	19.9%	1.83 (0.61, 5.50)	2014
Total (95%CI)		294		356	100.0%	2.75 (1.75, 4.30)	
Total events	122		111				

Heterogeneity: χ^2 = 10.54, *df* = 6 (*P* = 0.10); I^2 = 43%

Test for overall effect: *Z* = 4.42 (*P* < 0.00001)

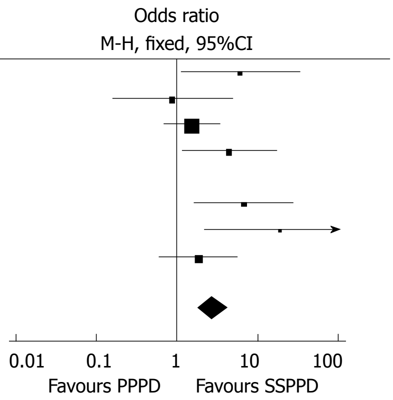


Figure 2 Forest plots demonstrating primary outcome. Forest plots illustrating results of delayed gastric emptying in the form of meta-analysis comparing PPPD with SSPPD. Pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated using the fixed-effects model. PPPD: Pylorus preserving pancreaticoduodenectomy; SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy.

Table 3 Summary results for studies comparing pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy

Outcome of interest	No. of studies	No. of patients	OR/WMD = (95%CI)	*P* value	Heterogeneity *P* value	I^2
Delayed gastric emptying	8	650	2.75 (1.75-4.30)	< 0.00001	0.10	43%
Operation time	8	650	-5.30 (-43.44-32.84)	0.79	0.0003	77%
Intraoperative blood loss	8	650	-217.70 [-429.77-(-5.63)]	0.04	0.004	68%
Pancreatic fistula	7	583	0.91 (0.56-1.49)	0.7	0.97	0%
Postoperative hemorrhage	5	461	0.51 (0.15-1.74)	0.29	0.95	0%
Intra-abdominal abscess	5	461	1.05 (0.54-2.05)	0.89	0.65	0%
Wound infection	5	394	0.88 (0.39-1.97)	0.75	0.88	0%
Time of start liquid diet	4	286	2.97 (-0.43-6.38)	0.09	0.001	82%
Time of start solid diet	4	316	3.69 (-0.46-7.83)	0.08	< 0.00001	91%
Time of nasogastric intubation	6	438	2.68 (0.77-4.58)	0.006	< 0.00001	96%
Reinsertion of nasogastric tube	4	349	1.90 (0.91-3.97)	0.09	0.58	0%
Mortality	6	471	0.31 (0.05-2.01)	0.22	1.00	0%
Hospital stay	4	255	3.92 (-0.37-8.22)	0.07	0.04	64%

WMD: Weight mean difference.

summarized in Table 4. The rate of DGE was also shown to be lower in the studies using the ISGPS definition (OR = 8.73; 95%CI: 2.09-36.56; *P* = 0.003), pancreaticojejunostomy (OR = 3.72; 95%CI: 2.12-6.56; *P* < 0.00001), RCTs (OR = 2.69; 95%CI: 1.17-6.17; *P* = 0.02) or non-RCTs (OR = 3.36; 95%CI: 1.25-9.08; *P* = 0.02).

Publication bias

The funnel plot based on the incidence of DGE is shown in Figure 4. None of the studies lies outside the limits of the 95%CI, indicating there was no evidence of publication bias.

DISCUSSION

Physiologically, gastric emptying requires coordination of the gastric antrum, pylorus and duodenum through paracrine messages and extrinsic stimulation from the vagus nerve[36]. DGE is one of the most common complications after pancreaticoduodenectomy and has been reported to occur in 1%-6% of patients[37]. While this is not a life-threatening complication of pancreatic surgery, it results in a reduced quality of life, impaired oral intake, increased hospital costs and the delayed initiation of adjuvant chemotherapy, where required. The pathogenesis of DGE after PPPD is thought to involve a number of factors, such as: gastric atony caused by vagotomy[38]; pylorospasm[39,40]; ischemia of the pylorus ring due to division of the right gastric artery[41]; congestion around the pylorus ring due to division of the left gastric vein[42]; and gastric dysrhythmia secondary to other complications such as pancreatic fisecon[43,44]. SSPPD was introduced in recent years as an alternative to PPPD to maintain the pooling ability of the stomach and reduce the incidence of DGE[17] by retaining most of the gastric body but resecting the pyloric complex itself. Whereas in a PPPD the proximal duodenum is divided 3 to 4 cm distal to the pylorus ring, in an SSPPD more than 95% of the stomach is preserved.

This meta-analysis of two RCTs and six non-randomized trials (prospective and retrospective) revealed a significant benefit of SSPPD compared with

Table 4 Sensitivity analysis performed for studies comparing pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy

Outcome of interest	No. of studies	No. of patients	OR (95%CI)	*P* value	Heterogeneity *P* value	I^2
DGE with ISGPS definition						
DGE (ISGPS B/C)	6	553	8.73 (2.09-36.56)	0.003	< 0.0001	82%
Operation time	6	553	6.50 (-35.02-48.02)	0.76	0.0005	80%
Intraoperative blood loss	6	553	0.78 (-81.90-83.46)	0.99	0.20	33%
Pancreatic fistula	5	486	0.92 (0.54-1.55)	0.75	0.93	0%
Postoperative hemorrhage	4	397	0.57 (0.15-2.16)	0.41	0.91	0%
Intraabdominal abscess	4	397	1.07 (0.53-2.18)	0.85	0.49	0%
Wound infection	3	297	1.18 (0.45-3.09)	0.74	0.98	0%
Time of start liquid diet	2	189	3.62 (-2.82-10.06)	0.27	0.03	80%
Time of start solid diet	3	252	4.77 (-0.11-9.64)	0.06	< 0.00001	94%
Time of nasogastric intubation	4	341	3.32 (0.31-6.32)	0.03	< 0.00001	97%
Reinsertion of nasogastric tube	3	285	2.15 (0.93-4.96)	0.07	0.44	0%
Mortality	4	374	0.32 (0.03-3.18)	0.33	0.97	0%
Hospital stay	3	222	5.96 (3.46-8.46)	< 0.00001	0.55	0%
DGE with other definition						
DGE	2	97	2.29 (0.35-15.21)	0.39	0.11	61%
Operation time	2	97	-48.51 (-109. 22-12.20)	0.12	0.79	0%
Intraoperative blood loss	2	97	-588.29 [-898.10-(-278.49)]	0.0002	0.79	0%
Pancreatic fistula	2	97	0.86 (0.22-3.33)	0.83	-	-
Wound infection	2	97	0.44 (0.09-2.08)	0.30	0.88	0%
Time of start liquid diet	2	97	2.30 (-2.30-6.91)	0.33	0.006	87%
Time of NGD insertion	2	97	1.82 (-2.43-6.06)	0.40	0.02	
Mortality	2	97	0.29 (0.01-7.26)	0.45	-	-
Hospital stay	2	97	0.17 (-2.77-3.11)	0.91	0.24	27%
Reconstruction with pancreaticojejunostomy						
DGE	6	471	3.72 (2.12-6.56)	< 0.00001	0.18	35%
Operation time	6	471	-11.79 (-32.26-8.68)	0.26	0.21	30%
Intraoperative blood loss	6	471	-265.87 (-422.93-108.81)	0.0009	0.15	38%
Pancreatic fistula	6	471	0.90 (0.55-1.48)	0.67	0.94	0%
Postoperative hemorrhage	4	349	0.61 (0.16-2.38)	0.48	0.93	0%
Intra-abdominal abscess	4	349	1.06 (0.51-2.22)	0.88	0.48	0%
Wound infection	4	327	0.83 (0.34-2.03)	0.68	0.78	0%
Time of start solid diet	3	249	2.29 (-1.97-6.54)	0.29	0.06	64%
Time of nasogastric intubation	5	371	1.92 (0.38-3.47)	0.01	< 0.00001	89%
Hospital stay	3	188	1.23 (-1.64-4.09)	0.40	0.25	28%
Reconstruction with pancreaticogastrostomy						
DGE	2	179	1.51 (0.70-3.26)	0.29	-	-
Operation time	2	179	49.00 (30.41-67.59)	< 0.00001	-	-
Intraoperative blood loss	2	179	41.00 (-51.78-133.78)	0.39	-	-
Randomized controlled trial						
DGE	2	230	2.69 (1.17-6.17)	0.02	0.32	0%
Operation time	2	230	-16.69 (-42.68-9.30)	0.21	0.83	0%
Intraoperative blood loss	2	230	-120.23 (-364.94-124.48)	0.34	0.77	0%
Pancreatic fistula	2	230	1.08 (0.53-2.20)	0.82	0.91	0%
Postoperative hemorrhage	2	230	0.67 (0.11-4.11)	0.67	0.72	0%
Intra-abdominal abscess	2	230	0.75 (0.14-4.14)	0.75	0.15	51%
Wound infection	2	230	1.19 (0.38-3.70)	0.76	0.86	0%
Reinsertion of nasogastric tube	2	230	2.17 (0.84-5.59)	0.11	0.20	39%
Mortality	2	230	0.34 (0.01-8.46)	0.51	-	-
Non-randomized controlled trial						
DGE	6	420	3.36 (1.25-9.08)	0.02	0.05	58%
Operation time	6	420	-0.56 (-47.55-46.43)	0.98	0.007	72%
Intraoperative blood loss	6	420	-283.77 (-593.42-25.87)	0.07	0.001	78%
Pancreatic fistula	5	353	0.77 (0.39-1.53)	0.46	0.93	0%
Postoperative hemorrhage	3	231	0.41 (0.08-2.22)	0.30	0.78	0%
Intra-abdominal abscess	3	231	1.21 (0.47-3.13)	0.70	0.83	0%
Wound infection	3	164	0.64 (0.19-2.08)	0.45	0.73	0%
Time of start liquid diet	3	186	3.68 (-0.30, 7.66)	0.07	0.0006	87%
Time of start solid diet	3	186	5.06 (0.39-9.73)	0.03	0.04	69%
Time of nasogastric intubation	5	308	3.49 (0.82-6.16)	0.01	< 0.00001	95%
Hospital stay	3	155	4.28 (-0.56-9.12)	0.08	0.02	76%
Mortality	4	240	0.30 (0.03-2.94)	0.30	0.97	0%

D1 lymph node dissection						
DGE	2	57	0.32 (0.07-1.48)	0.14	0.90	0%
D2 lymph node dissection						
DGE	2	119	3.07 (1.05-9.02)	0.04	0.53	0%

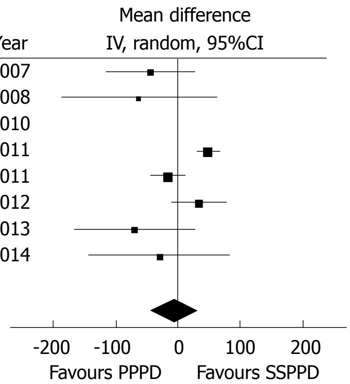
SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; WMD: Weighted mean difference.

A

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Hayashibe 2007	450.5	63.8	12	494.5	138.9	21	13.4%	-44.00 (-113.51, 25.51)	2007
Akizuki 2008	457	236.3	34	520	268.3	30	6.7%	-63.00 (-187.60, 61.60)	2008
Kurahara 2010	460.6	0	48	545	0	64		Not estimable	2010
Oida 2011	464	39	25	415	35	42	22.8%	49.00 (30.41, 67.59)	2011
Kawai 2011	342	71	64	358	84	66	21.5%	-16.00 (-42.71, 10.71)	2011
Fujii 2012	488	98	33	455	107	56	18.3%	33.00 (-10.63, 76.63)	2012
Nanashima 2013	540	148	28	610	209	27	9.5%	-70.00 (-166.02, 26.02)	2013
Matsumoto 2014	523	285.3	50	552	290.3	50	7.7%	-29.00 (-141.82, 83.82)	2014
Total (95%CI)			294			356	100.0%	-5.30 (-43.44, 32.84)	

Heterogeneity: Tau^2 = 1573.21; χ^2 = 25.68, *df* = 6 (*P* = 0.0003); I^2 = 77%

Test for overall effect: *Z* = 0.27 (*P* = 0.79)

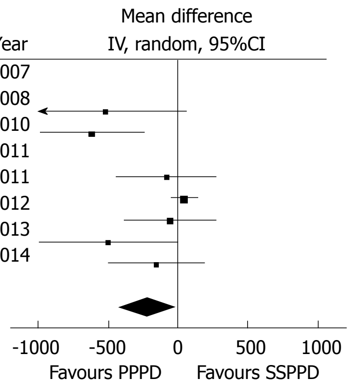


B

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Hayashibe 2007	1321.7	682	12	1843.2	987.7	21	8.7%	-521.50 (-1093.65, 50.65)	2007
Akizuki 2008	619	565	34	1235	882.5	30	13.8%	-616.00 (-984.50, -247.50)	2008
Kurahara 2010	1084.6	0	48	1779.5	0	64		Not estimable	2010
Kawai 2011	820	987	64	902	1075	66	14.3%	-82.00 (-436.59, 272.59)	2011
Oida 2011	600	196	25	559	172	42	22.7%	41.00 (-51.78, 133.78)	2011
Fujii 2012	1225	728	33	1284	821	56	15.1%	-59.00 (-387.53, 269.53)	2012
Nanashima 2013	1306	776	28	1810	1054	27	10.5%	-504.00 (-994.58, -13.42)	2013
Matsumoto 2014	826	645.8	50	981	1035	50	14.8%	-155.00 (-493.15, 183.15)	2014
Total (95%CI)			294			356	100.0%	-217.70 (-429.77, -5.63)	

Heterogeneity: Tau^2 = 49231.24; χ^2 = 18.98, *df* = 6 (*P* = 0.004); I^2 = 68%

Test for overall effect: *Z* = 2.01 (*P* = 0.04)

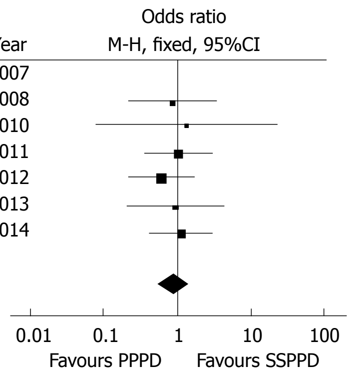


C

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Hayashibe 2007	0	12	0	21		Not estimable	2007
Akizuki 2008	5	34	5	30	13.5%	0.86 (0.22, 3.33)	2008
Kurahara 2010	1	48	1	64	2.5%	1.34 (0.08, 21.99)	2010
Kawai 2011	8	64	8	66	20.6%	1.04 (0.36, 2.95)	2011
Fujii 2012	7	33	17	56	29.7%	0.62 (0.22, 1.70)	2012
Nanashima 2013	4	28	4	27	10.4%	0.96 (0.21, 4.29)	2013
Matsumoto 2014	11	50	10	50	23.3%	1.13 (0.43, 2.96)	2014
Total (95%CI)		269		314	100.0%	0.91 (0.56, 1.49)	
Total events	36		45				

Heterogeneity: χ^2 = 0.90, *df* = 5 (*P* = 0.97); I^2 = 0%

Test for overall effect: *Z* = 0.38 (*P* = 0.70)

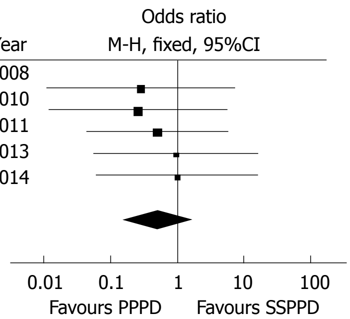


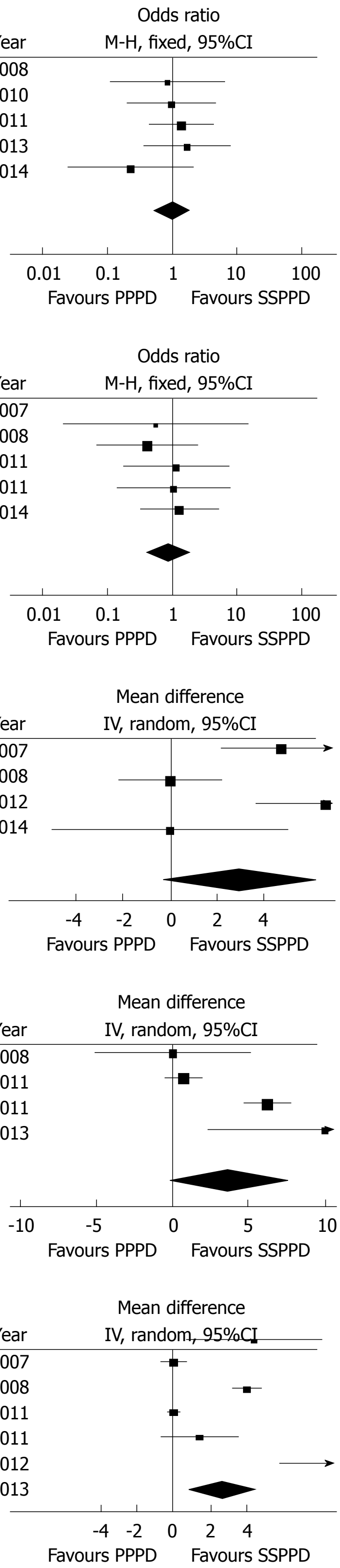
D

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Akizuki 2008	0	34	1	30	20.6%	0.29 (0.01, 7.26)	2008
Kurahara 2010	0	48	2	64	28.0%	0.26 (0.01, 5.49)	2010
Kawai 2011	1	64	2	66	25.5%	0.51 (0.04, 5.74)	2011
Nanashima 2013	1	28	1	27	12.9%	0.96 (0.06, 16.21)	2013
Matsumoto 2014	1	50	1	50	12.9%	1.00 (0.06, 16.44)	2014
Total (95%CI)		224		237	100.0%	0.51 (0.15, 1.74)	
Total events	3		7				

Heterogeneity: χ^2 = 0.73, *df* = 4 (*P* = 0.95); I^2 = 0%

Test for overall effect: *Z* = 1.07 (*P* = 0.29)





E

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Akizuki 2008	2	34	2	30	11.9%	0.88 (0.12, 6.63)	2008
Kurahara 2010	3	48	4	64	19.1%	1.00 (0.21, 4.69)	2010
Kawai 2011	8	64	6	66	30.7%	1.43 (0.47, 4.38)	2011
Nanashima 2013	5	28	3	27	14.9%	1.74 (0.37, 8.12)	2013
Matsumoto 2014	1	50	4	50	23.3%	0.23 (0.03, 2.18)	2014
Total (95%CI)		224		237	100.0%	1.05 (0.54, 2.05)	
Total events	19		19				

Heterogeneity: χ^2 = 2.48, *df* = 4 (*P* = 0.65); I^2 = 0%
Test for overall effect: *Z* = 0.14 (*P* = 0.89)

F

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Hayashibe 2007	0	12	1	21	8.5%	0.55 (0.02, 14.48)	2007
Akizuki 2008	2	34	4	30	31.6%	0.41 (0.07, 2.40)	2008
Oida 2011	2	25	3	42	16.3%	1.13 (0.18, 7.28)	2011
Kawai 2011	2	64	2	66	15.1%	1.03 (0.14, 7.56)	2011
Matsumoto 2014	5	50	4	50	28.5%	1.28 (0.32, 5.07)	2014
Total (95%CI)		185		209	100.0%	0.88 (0.39, 1.97)	
Total events	11		14				

Heterogeneity: χ^2 = 1.19, *df* = 4 (*P* = 0.88); I^2 = 0%
Test for overall effect: *Z* = 0.31 (*P* = 0.75)

G

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Hayashibe 2007	14.7	4.2	12	10	2	21	27.1%	4.70 (2.17, 7.23)	2007
Akizuki 2008	5	4.8	34	5	4	30	28.2%	0.00 (-2.16, 2.16)	2008
Fujii 2012	15.2	7.8	33	8.6	4.7	56	25.8%	6.60 (3.67, 9.53)	2012
Matsumoto 2014	5	11.3	50	5	14	50	18.9%	0.00 (-4.99, 4.99)	2014
Total (95%CI)			129			157	100.0%	2.97 (-0.43, 6.38)	

Heterogeneity: Tau^2 = 9.47; χ^2 = 16.31, *df* = 3 (*P* = 0.0010); I^2 = 82%
Test for overall effect: *Z* = 1.71 (*P* = 0.09)

H

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Akizuki 2008	7	9.8	34	7	10.8	30	21.9%	0.00 (-5.08, 5.08)	2008
Kawai 2011	6.3	3.7	64	5.6	3.3	66	31.7%	0.70 (-5.01, 1.91)	2011
Oida 2011	16.4	3.6	25	10.2	2	42	31.1%	6.20 (4.66, 7.74)	2011
Nanashima 2013	19	16	28	9	13	27	15.3%	10.00 (2.31, 17.69)	2013
Total (95%CI)			151			165	100.0%	3.69 (-0.46, 7.83)	

Heterogeneity: Tau^2 = 13.74; χ^2 = 35.01, *df* = 3 (*P* < 0.00001); I^2 = 91%
Test for overall effect: *Z* = 1.74 (*P* = 0.08)

I

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Hayashibe 2007	10.5	6.4	12	6.1	1.3	21	11.6%	4.40 (0.74, 8.06)	2007
Akizuki 2008	1	0.8	34	1	1.8	30	19.7%	0.00 (-0.70, 0.70)	2008
Oida 2011	5.6	1.9	25	1.6	0.7	42	19.6%	4.00 (3.23, 4.77)	2011
Kawai 2011	0.6	0.9	64	0.6	1	66	20.1%	0.00 (-0.33, 0.33)	2011
Fujii 2012	2.7	6.1	33	1.3	0.7	56	16.3%	1.40 (-0.69, 3.49)	2012
Nanashima 2013	15	7	28	6	5	27	12.9%	9.00 (5.79, 12.21)	2013
Total (95%CI)			196			242	100.0%	2.68 (0.77, 4.58)	

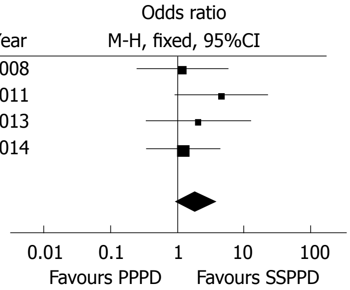
Heterogeneity: Tau^2 = 4.67; χ^2 = 120.92, *df* = 5 (*P* < 0.00001); I^2 = 96%
Test for overall effect: *Z* = 2.75 (*P* = 0.006)

J

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Akizuki 2008	4	34	3	30	26.3%	1.20 (0.25, 5.85)	2008
Kawai 2011	8	64	2	66	16.1%	4.57 (0.93, 22.43)	2011
Nanashima 2013	4	28	2	27	16.3%	2.08 (0.35, 12.45)	2013
Matsumoto 2014	6	50	5	50	41.2%	1.23 (0.35, 4.32)	2014
Total (95%CI)		176		173	100.0%	1.90 (0.91, 3.97)	
Total events	22		12				

Heterogeneity: χ^2 = 1.97, *df* = 3 (*P* = 0.58); I^2 = 0%

Test for overall effect: *Z* = 1.71 (*P* = 0.09)

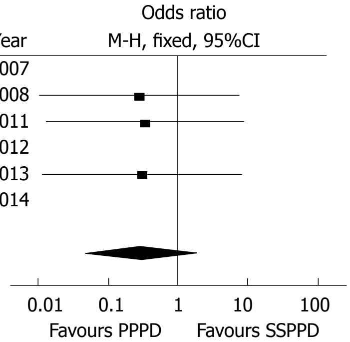


K

Study or subgroup	PPPD Events	PPPD Total	SSPPD Events	SSPPD Total	Weight	Odds ratio M-H, fixed, 95%CI	Year
Hayashibe 2007	0	12	0	21		Not estimable	2007
Akizuki 2008	0	34	1	30	34.6%	0.29 (0.01, 7.26)	2008
Kawai 2011	0	64	1	66	32.3%	0.34 (0.01, 8.46)	2011
Fujii 2012	0	33	0	56		Not estimable	2012
Nanashima 2013	0	28	1	27	33.1%	0.31 (0.01, 7.95)	2013
Matsumoto 2014	0	50	0	50		Not estimable	2014
Total (95%CI)		221		250	100.0%	0.31 (0.05, 2.01)	
Total events	0		3				

Heterogeneity: χ^2 = 0.01, *df* = 2 (*P* = 1.00); I^2 = 0%

Test for overall effect: *Z* = 1.23 (*P* = 0.22)



L

Study or subgroup	PPPD Mean	PPPD SD	PPPD Total	SSPPD Mean	SSPPD SD	SSPPD Total	Weight	Mean difference IV, random, 95%CI	Year
Hayashibe 2007	33.1	4	12	32.5	4.7	21	39.6%	0.60 (-2.43, 3.63)	2007
Oida 2011	30	6.2	25	24.1	3.1	42	41.8%	5.90 (3.30, 8.50)	2011
Nanashima 2013	42	18	28	31	26	27	10.4%	11.00 (-12.68, 14.68)	2013
Matsumoto 2014	38	32.3	50	37	37.3	50	8.2%	1.00 (-12.68, 14.68)	2014
Total (95%CI)			115			140	100.0%	3.92 (-0.37, 8.22)	

Heterogeneity: Tau^2 = 9.73; χ^2 = 8.37, *df* = 3 (*P* = 0.04); I^2 = 64%

Test for overall effect: *Z* = 1.79 (*P* = 0.07)

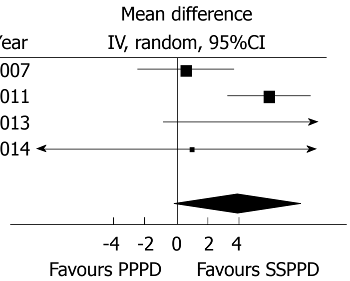


Figure 3 Forest plots demonstrating secondary outcomes. Forest plots illustrating results of operation time (A), intraoperative blood loss (B), pancreatic fistula (C), postoperative hemorrhage (D), intraabdominal abscess (E), wound infection (F), time to starting liquid diet (G), time to starting solid diet (H), period of nasogastric intubation (I), reinsertion of nasogastric tube (J), mortality (K), hospital stay (L) in the form of meta-analysis comparing PPPD with SSPPD. Pooled odds ratios (ORs) or weighted mean difference (WMD) with 95% confidence intervals (CI) were calculated using the fixed effects model or the random-effects model. PPPD: Pylorus preserving pancreaticoduodenectomy; SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy.

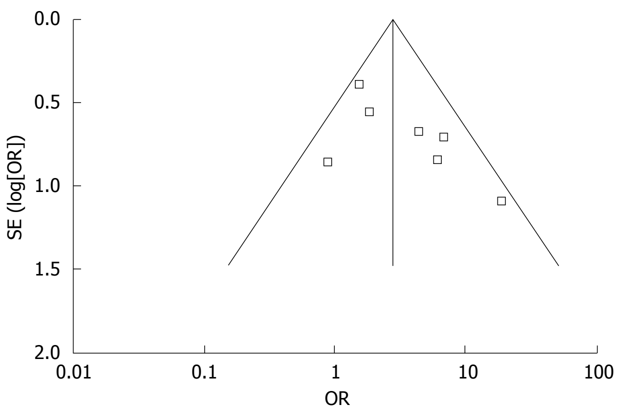


Figure 4 Funnel plot to investigate publication bias. Funnel plot on delayed gastric emptying basing on all studies. The funnel plot revealed no publication bias.

PPPD with regard to DGE and period of nasogastric intubation, albeit with greater intraoperative blood loss. Subgroup analysis specifically looking at trials using the ISGPS definition of DGE, reconstruction with pancreaticojejunostomy, RCTs or non-randomized trials also favored SSPPD with lower rates of DGE. This is the first complete pooled study to date comparing rates of DGE with the two surgical techniques (SSPPD *vs* PPPD). Apart from obvious potential benefits relating to hospital stay, nutrition and possible quality of life benefits, SSPPD may even lead to shorter postoperative recovery times and even earlier commencement of oral chemotherapy, where required. As a result, we consider SSPPD to have distinct short-term advantages over PPPD.

Due to the lack of an internationally accepted consensus definition for DGE in the past, the differences in reported DGE rates may have reflected differences in definitions rather than true differences in incidence. The ISGPS proposed definition of DGE, which includes a 3 tiered clinical grading system[45] based on clinical impact, allows more accurate comparisons. DGE grades B and C signify a prolonged hospital stay and increased costs. In our subgroup analysis, DGE grades B and C were lower in the SSPPD group compared to the PPPD group.

Previous studies have often found associations between DGE and postoperative intraabdominal complications such as biliary fistula, pancreatic fistula, and intraabdominal abscess[16,29,42,46], although causality has never been clearly demonstrated. Our systematic review did not reveal any significant differences between SSPPD and PPPD in the incidence of pancreatic fistula or intraabdominal abscess rates, suggesting that these did not have a simple relationship with DGE.

Coordination of the antro-pyloric region is considered to be impaired after surgery involving lymph node dissection in the area of the hepatoduodenal ligament and can lead to a physiological derangement similar to that seen with truncal vagotomy[39]. In our subgroup analysis, however, degree of nodal dissection (D1 *vs* D2) did not influence rates of DGE, although the sample size was very small.

Importantly, our study found no statistically significant differences in mortality, post-operative hemorrhage, pancreatic fistula or wound infection rates between the two operative techniques. While time to commencing liquid and solid diet and hospital stay were also not statistically significant, there is a clear tendency favoring SSPPD in relation to these outcomes. It is notable, however, that there seems to be the greatest difference in the retrospective and non-randomized trials, raising the possibility of selection bias. One can envisage, for example, a surgical team introducing diet earlier in patients who underwent SSPPD *vs* PPPD. Furthermore, it is worth noting that there was no mortality at all in any of the included PPPD groups, whereas there were reports of single patient mortality in the SSPPD groups. While this difference did not reach statistical significance, one has to note that none of the studies were sufficiently powered to detect small differences in infrequent events such as death and this must be addressed in any future randomized controlled trial.

There are a number of limitations to this study. Firstly, all included studies originated from Japan, which may skew both the population under investigation as well as operative techniques. Also, most included studies were non-randomized and retrospective in design. Furthermore, there was significant variability in clinical parameters such as operative time, intraoperative blood loss, time of start of liquid or solid diet, time of nasogastric intubation and hospital stay. This was likely related to the differences in operative technique (pancreaticojejunostomy *vs* pancreaticogastrostomy, end-to-end *vs* end-to-side anastomoses, use of pancreatic stents). Due to a lack of detailed information in the included studies, it was not possible to perform a subgroup analysis based on various reconstruction approaches. The greatest shortcoming, however, is that the studies included provided us with insufficient information to conduct a sound comparison of long-term nutritional status, gastrointestinal function and quality of life. Clearly, if there were to be significant long-term complications such as increased rates in dumping syndrome, it would argue strongly against SSPPD as a technique.

In conclusion, this study suggests SSPPD is as safe as PPPD in the studied population and may be superior to PPPD with respect to DGE. However, there is an evident need for well-designed RCTs comparing SSPPD and PPPD with respect to quality of life and survival outcomes.

COMMENTS

Background

Currently, classic pancreaticoduodenectomy and pylorus preserving pancreaticoduodenectomy (PPPD) are considered to be the most widely used surgical procedures for the treatment of pancreatic head and periampullary tumors. Delayed gastric emptying (DGE) is regarded as one of the most common postoperative complications in these two surgical approaches. Recently, a new surgical method, subtotal stomach-preserving pancreaticoduodenectomy (SSPPD), was developed to reduce the incidence of DGE. However, whether this can be achieved in practice is not clear.

Research frontiers

To conduct a meta-analysis comparing perioperative outcomes, especially DGE, after PPPD and SSPPD for the first time.

Innovations and breakthroughs

Based on this meta-analysis, patients undergoing SSPPD had a significantly lower rate of DGE and a shorter period of nasogastric intubation despite being associated with greater intraoperative blood loss.

Applications

SSPPD can reduce DGE as well as improve short-term postoperative outcomes compared with PPPD. However, future randomized trials should compare the advantages between SSPPD and PPPD.

Peer-review

This report was of great interest because it seems to be the first complete pooled study to compare rates of DGE with the two surgical techniques, SSPPD *vs* PPPD. Of course there are limitations in that most of the studies included in this study were retrospective. However, this study can be the chart for deciding the surgical management for patients requiring pancreaticoduodenectomy and for further studies.

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