A Systematic Review and Meta-analysis of Pylorus-preserving Versus Classical Pancreaticoduodenectomy for Surgical Treatment of Periampullary and Pancreatic Carcinoma

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Objective: Comparison of effectiveness between the pylorus-preserving pancreaticoduodenectomy ("pylorus-preserving Whipple" [PPW]) and the classic Whipple (CW) procedure.

Methods: A systematic literature search (Medline, Embase, Cochrane Library, Biosis, Science Citation Index, Ovid Journals) was performed to identify all eligible articles. Randomized controlled trials (RCTs) comparing PPW versus CW for periampullary and pancreatic carcinoma were eligible for inclusion. The methodologic quality of included studies was evaluated independently by 2 authors. Quantitative data on perioperative parameters (blood loss, transfusion, operation time, and length of hospital stay), mortality, morbidity, and survival were extracted from included studies for meta-analysis. Pooled estimates of overall treatment effect were calculated using a random effects model.

Results: In total, 1235 abstracts were retrieved and checked for eligibility and 6 RCTs finally included. The critical appraisal revealed vast heterogeneity with respect to methodologic quality and outcome parameters. The comparison of overall in-hospital mortality (odds ratio, 0.49; 95% CI, 0.17 to 1.40; $P = 0.18$), morbidity (odds ratio 0.89; 95% CI, 0.48 to 1.62; $P = 0.69$), and survival (hazard ratio, 0.74; 95% CI, 0.52 to 1.07; $P = 0.11$) showed no significant difference. However, operating time (weighted mean difference, −68.26 minutes; 95% CI, −105.70 to −30.83; $P = 0.0004$), and intraoperative blood loss (weighted mean difference, −766 mL; 95% CI, −965.26 to −566.74; $P = 0.00001$) were significantly reduced in the PPW group.

Conclusion: Hence, in the absence of relevant differences in mortality, morbidity, and survival, the PPW seems to be as effective as the CW. Given obvious clinical and methodological interstudy heterogeneity, efforts should be intensified in the future to perform high quality RCTs of complex surgical interventions on the basis of well defined outcome parameters.

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Pancreatic cancer is the fourth leading cause of cancer death in men and the fifth in women, accounting for 4.8% and 5.5% of cancer deaths in men and women, respectively.[1,2] As shown in large case series,[3] the aggressive biology of these tumors and the high local recurrence rate in combination with the early metastatic spread lead to 5-year survival rates between 11% and 21% after resection.[4]

Surgical resection by means of pancreaticoduodenectomy provides the only chance of cure for patients with periampullary and pancreatic carcinoma.[4–6] Advances in surgical technique have reduced the operative mortality rate to below 5% in high-volume centers.[6–8] Nevertheless, operative morbidity remains high, occasionally approaching 30% to 40%,[9–11] most often including pancreatic fistula, intra-abdominal abscesses, sepsis, and delayed gastric emptying (DGE).

Two operation techniques are performed predominantly in the treatment of periampullary and pancreatic head cancer: the classic Whipple operation (CW) developed by Kausch[12] and Whipple[13] and the pylorus-preserving Whipple procedure (PPW) inaugurated by Watson[14] and popularized by Traverso and Longmire.[15]

The CW operation consists of an en bloc removal of the pancreatic head, the duodenum, the common bile duct, the gall bladder, and the distal portion of the stomach together with the adjacent lymph-nodes.[16] This operation can lead to specific complications such as early and late dumping, postoperative weight loss,[17] and postoperative reflux.[18] Leaving the functioning pylorus at the gastric outlet, the PPW represents a surgical alternative that is being performed by an increasing number of surgeons.

Which is the better technique? This question is still being debated. Some authors suggested possible advantages of the PPW procedure in terms of reduced operation time,[19] less blood loss, better access to the biliary anastomosis for postoperative endoscopy in patients with recurrent biliary obstruction, improved postoperative weight gain,[17] and higher quality of life.[20] On the other hand, the reported incidence of early DGE seemed to be higher in the PPW group in previous series.[21–23] Moreover, it has not been unequivocally shown that the lesser trauma induced by a PPW, beneficial as it may be to the patient, is yet oncologically adequate.

The inconclusive results of several nonrandomized studies have triggered a number of randomized controlled trials (RCTs). A qualitative appraisal and statistical aggregation of the individual RCTs that will give a more precise estimate of the treatment effect is still lacking, as systematic reviews of high quality primary studies represent, if rigorously performed, the highest level of evidence.[24]

The primary objective of this study is to analyze the existing evidence regarding the PPW and CW procedures in a systematic review (SR) and to provide a meta-analysis (MA) of perioperative parameters (blood loss, transfusion, operation time), postoperative mortality and morbidity, length of hospital stay, and survival.

METHODS

The rationale and design of this study were prepared according to the described methodology[25] and approved by peer-review of the Cochrane Collaboration (Upper Gastrointestinal and Pancreatic Diseases Group, Leeds, UK).

Databases searched included the Cochrane Library Central (Register of Controlled Trials; 2005 Issue 4), Medline (1966 to November Week 3 2005), Premedline (Ovid), Journals Ovid (update November 28, 2005), Embase (1974 to December 2005), Biosis (1989 to December 2005) and the Science Citation Index Database (1945 to December 2005). Also searched were reference lists of retrieved relevant articles for additional trials. Moreover, investigators and experts in the field of pancreatic surgery were contacted to ensure that all relevant studies were identified. The search was not restricted to specific languages or years of publication. The last search was carried out on December 12, 2005.

Search Strategy

The search strategy in Medline (PubMed) was based on the following search terms (Medical Subject Heading terms and text words) with the appropriate combinations:

(Pylorus preserv* OR whipple OR pancreat* resection OR pancreatojejunostom* OR pancreaticojejunostom* OR pancreaticojejunostomy [MeSH] pancreatoduodenectom* OR pancreaticoduodenectom* OR pancreaticoduodenectomy [MeSH] OR duodenopancreatectom* OR pancreatectom* OR pancreatectomy [MeSH])

AND

(Adenocarcinom* panc* OR panc* tumor* OR panc* carc* OR panc* cancer* OR panc* neoplas* OR Pancreatic Neoplasm [MeSH])

AND

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] NOT (animal [mh] NOT human [mh])).

Study Selection

RCTs comparing CW versus PPW for periampullary and pancreatic carcinoma were eligible for this SR. Only RCTs reporting on the following outcomes were selected for data extraction: quantitative data on perioperative parameters (blood loss, transfusion, operation time, length of hospital stay), postoperative mortality and morbidity, and survival.

Two authors (M.K.D. and C.H.) independently identified and screened the search findings for potentially eligible RCTs. Abstracts and full articles were obtained for detailed evaluation and eligible trials were included into the SR. Any disagreements during the selection process were resolved by discussion with a third author (C.M.S.).

Data Extraction and Analysis

According to international recommendations,[26,27] the methodologic quality of RCTs was assessed using a standardized form to extract prespecified parameters.[28] Thus, the critical appraisal of the extracted data included rating of the randomization procedure, allocation concealment, sample size, consistency of the study population, length and quality of follow-up, rate of patients lost to follow-up, and statistical analysis of individual trials.

Two authors (M.K.D. and C.H.) independently extracted quantitative data on perioperative parameters, postoperative mortality, morbidity, and survival (Table 1). The synchronized extraction results were pooled as estimates of overall treatment effects in a MA and presented as weighted odds ratios (OR) for parameters of mortality and morbidity, weighted mean difference (WMD), a weighted average of the differences in means, for perioperative parameters and the corresponding 95% confidence intervals (CI). Data for the pooled overall survival were generated by extracting events

TABLE 1. Study Selection Criteria/Inclusion Criteria

Randomized controlled study design
Study population: pancreatic and periampullary carcinoma
Comparison of pylorus-preserving Whipple procedure and classical Whipple procedure
Quantitative data on postoperative mortality and morbidity
Anastomotic leakage
Pancreatic fistula
Delayed gastric emptying
Hemorrhage
Biliary leakage
Wound infection
Relaparotomy
Survival
Quantitative data on perioperative parameters
Operation time
Intraoperative blood loss
Replacement with red blood cell concentrates
Radicality of resection (R0 resection)
Positive lymph node status
Somatostatin application
Erythromycin application
Duration of hospital stay

(Kaplan-Meier curves) and calculating logarithmic hazard ratios (±standard error) using the corresponding P value (log-rank test).[29] The weight of each study relates to its sample size and study quality. All results were investigated for clinical and statistical heterogeneity. Clinical heterogeneity was defined as the existence of inhomogeneous study population, the variability of interventions, and the insufficient definition of outcome parameters or major variance in perioperative management. Clinical heterogeneity was explained where appropriate and possible. Statistical heterogeneity was explored by inspecting the forest plot and I^2 statistic. To account for clinical heterogeneity (varying or missing definitions of outcome parameters), overall estimates were calculated by using the random effects models[30] (Review Manager, Version 4.2 for Windows, Cochrane Collaboration, 2003). For this reason, the results of the MA are presented as more conservative estimates compared with an analysis with a fixed effect model in absence of clinical heterogeneity.[31]

RESULTS

Excluded Studies

The systematic literature search retrieved 1235 abstracts. During this process of study selection, 1211 screened abstracts had to be excluded. Of the remaining 24 screened full articles, 18 did not fulfill the inclusion criteria. Most of the excluded articles did not cover surgical aspects of the comparison of PPW and CW nor provide quantitative data on the prespecified outcome parameters (Table 2; Fig. 1).

Included Studies

Six RCTs[20,32–36] involving 578 randomized patients were eligible. Because of a per-protocol analysis of 5 trials,[20,32,33,35,36] quantitative data of 465 analyzed patients comparing the PPW (229 patients) and the CW (236 patients) procedure were found suitable for the SR (Table 3) and MA (Figs. 2, 3).

TABLE 2. Characteristics of Trials Excluded From Systematic Review and Reason for Exclusion (Screened Full Articles)

Study	Study Design	Compared Intervention	Reason for Exclusion
Farnell et al[45]	RCT	Pancreaticoduodenectomy with or without extended lymphadenectomy	No comparison of PPW and CW
Bell et al[46]	Narrative review	PPW vs. CW	Narrative Review of one included RCT[34]
Wagner et al[47]	Prospective cohort study	Multivariate analysis of outcome parameters of PPW, CW, palliative bypass, left resection, total pancreatectomy	Nonrandomized study design
Nguyen et al[48]	RCT	PPW vs. CW	Identical study collective as Yeo et al[44]; no additional information.
Shan et al[49]	RCT	PPW with or without octreotide application	No comparison of PPW and CW
Seiler et al[17]	RCT	PPW vs. CW	Long-term results available[33]; no additional information
Lin et al[50]	RCT	PPW vs. CW	Long-term results available[32]; no additional information
Yeo et al[43]	RCT	Pancreaticoduodenectomy with standard lymphadenectomy vs. extended lymphadenectomy	Study randomized not for the comparison of PPW vs. CW
Yeo et al[45]	RCT	Pancreaticoduodenectomy with standard lymphadenectomy vs. extended lymphadenectomy	Long term results of Yeo et al[43] (1999)
Pedrazzoli et al[51]	RCT	Pancreaticoduodenectomy with or without extended lymphadenectomy	No comparison of PPW and CW
Berge Henegouwen et al[52]	Prospective cohort study	PPW vs. CW	Nonrandomized study design; insufficient quantitative outcome parameters
Chou et al[53]	RCT	Invaginating pancreaticojejunostomy vs. duct to mucosa anastomosis for reconstruction	No comparison of PPW and CW
Brennan et al[54]	RCT	Postoperative total enteral nutrition vs. parenteral nutrition	No comparison of PPW vs. CW
Friess et al[55]	RCT	Postoperative complications following pancreatic surgery with or without application of octreotide	No comparison of PPW vs. CW
Bassi et al[56]	RCT	Postoperative complications following pancreatic surgery with or without application of octreotide	No comparison of PPW vs. CW
Johnstone et al[57]	RCT	Intraoperative radiotherapy vs. external beam radiotherapy following pancreatic resection	No comparison of PPW vs. CW
Bakkevold et al[58]	Prospective cohort study	Analysis of morbidity and mortality after radical and palliative pancreatic cancer surgery	Nonrandomized study design; no comparison of PPW vs. CW
Büchler et al[59]	RCT	Postoperative complications following pancreatic surgery with or without application of octreotide	No comparison of PPW vs. CW

Besides obvious variation in the sample size (range from 36[32] to 240[33]) the evaluation of the study population baseline data revealed adequate consistency: all analyzed patients were included because of resectable pancreatic or periampullary cancer. Moreover, 4 studies[20,33,34,36] provided data on resection margin status following PPW or CW, respectively: all studies showed a balanced interstudy and intrastudy distribution of R0 resections (mean R0 resection, 91.1% [PPW]; 90.4% [CW]). In addition, we observed a similar distribution of positive lymph node status in 3 studies (mean positive lymph node status: 54.4% [PPW]; 60.3% [CW]).[20,33,34]

The methodologic appraisal of the single studies revealed considerable heterogeneity in study design. Only 2 trials, the largest (170[34] and 240[33] patients, respectively) described the underlying sample size calculation, whereas 4 trials[20,32,35,36] did not justify the number of included patients.

The randomization process was described in 3 trials,[33,34,36] the 3 others[20,32,35] did not specify the process of random allocation adequately. Only 2 trials[33,34] described how allocation concealment was maintained and blinded outcome assessment was performed.

The trials by Seiler et al[33] and Tran et al[34] provided the most comprehensive definitions. Four trials[20,32,35,36] did not specify the criteria of their endpoints adequately.

Follow-up quality was evaluated by assessing the follow-up sequence and the length of follow-up. Median follow-up varied from 18 months[35] up to 144 months;[36] one study[32] did not report and specify on the follow-up at all.

Statistical analysis was performed in one trial[34] according to the intention-to-treat principle; 5 trials[20,32,33,35,36] applied a per-protocol analysis.

Regarding the perioperative management, we observed a nonstandardized administration of somatostatin as to dosage, route, frequency, and length. Two of the 6 RCTs reported the use of octreotide (100–200 μg).[33,34] Most of the trials discarded the use of erythromycin[33,34] or did not mention its perioperative application.[20,32,35,36]

Meta-Analysis of Mortality, Morbidity, Perioperative Parameters, and Survival

Six studies[20,32–36] provided quantitative data on overall mortality and morbidity in addition to rates of pancreatic fistula, wound infection, postoperative bleeding, DGE, and biliary leakage following the PPW and the CW procedures, respectively.

Mortality and Overall Morbidity

Both mortality and postoperative overall morbidity showed similar ranges in the PPW group (mortality, 0%[35] to 7.1%;[32] morbidity, 20.8%[20] to 59%[36]) and the CW group (mortality, 0%[32,35] to 7%;[34] morbidity, 20.8%[20] to 68.2%[33]), respectively.

Four RCTs,[20,33,35,36] including 262 analyzed patients, were suitable for analysis of overall postoperative morbidity; no significant difference was noted: 47.6% (PPW) versus 52.2% (CW) (OR, 0.89; 95% CI, 0.48 to 1.62; $P = 0.69$; I^2 test, 22.1% data heterogeneity) (Table 4; Fig. 2).

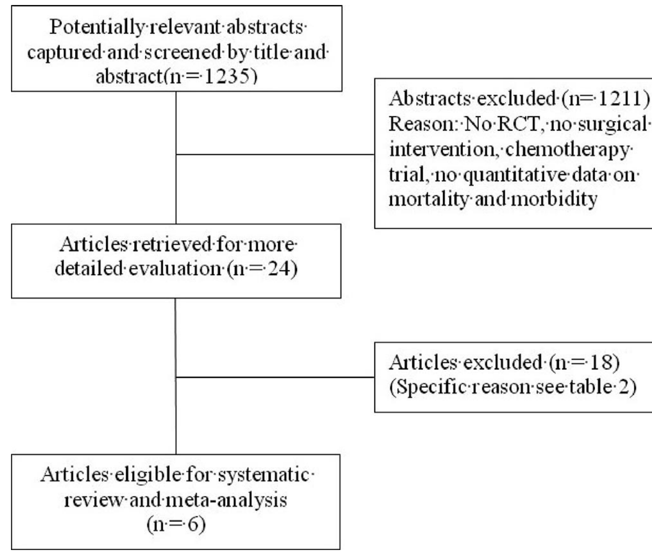

FIGURE 1. Number of abstracts and articles identified and evaluated during the review process. Modified flow chart according to Quorom.[28]

The overall effect estimate of 205 (PPW) versus 212 (CW) patients revealed no difference in mortality (OR, 0.49; 95% CI, 0.17 to 1.40; $P = 0.18$; I^2 test, 0% data heterogeneity).

Perioperative Parameters

MA of perioperative parameters such as blood loss, red blood cell transfusion, operating time, and length of hospital stay of 3 RCTs[20,32,35] demonstrated a significant reduction of operating time [min] for the PPW (WMD, −68.26; 95% CI, −105.70 to −30.83; $P = 0.0004$; I^2 test, 67.5% data heterogeneity). Intraoperative blood loss (mL) could be extracted in an analyzable way from only one trial[32] and was significantly reduced in the PPW group (WMD, −766.00; 95% CI, −965.26 to −566.74; $P < 0.00001$). In contrast, the summarized effect estimate of blood replacement (units) indicated similar application of blood products intraoperatively (WMD, −0.65; 95% CI, −1.92 to 0.61; $P = 0.31$; I^2 test, 0% data heterogeneity). Length of hospital stay (days) showed similar results in both groups (WMD, −1.80; 95% CI, −8.94 to 5.34; $P = 0.62$), with only one article providing adequate data for pooling[20] (Fig. 3).

Parameters of Morbidity

Data on pancreas associated morbidity were inconclusive due to broad ranges of rates for DGE, occurrence of pancreatic fistula, and biliary leakage (Table 4). To further differentiate the underlying heterogeneity, MA of these parameters was performed.

Five studies[32–36] provided data on the occurrence of DGE. Given statistical heterogeneity (I^2 test 75.6%), 3 studies[32,35,36] were in favor of CW, one in favor of PPW,[33] whereas one study[34] presented an equal rate of DGE. Pooling of these individual results revealed 59 patients of 203 (29.0%) in the PPW group compared with 51 of 209 (24.4%) in the CW group (OR, 2.35; 95% CI, 0.72 to 7.61; $P = 0.16$).

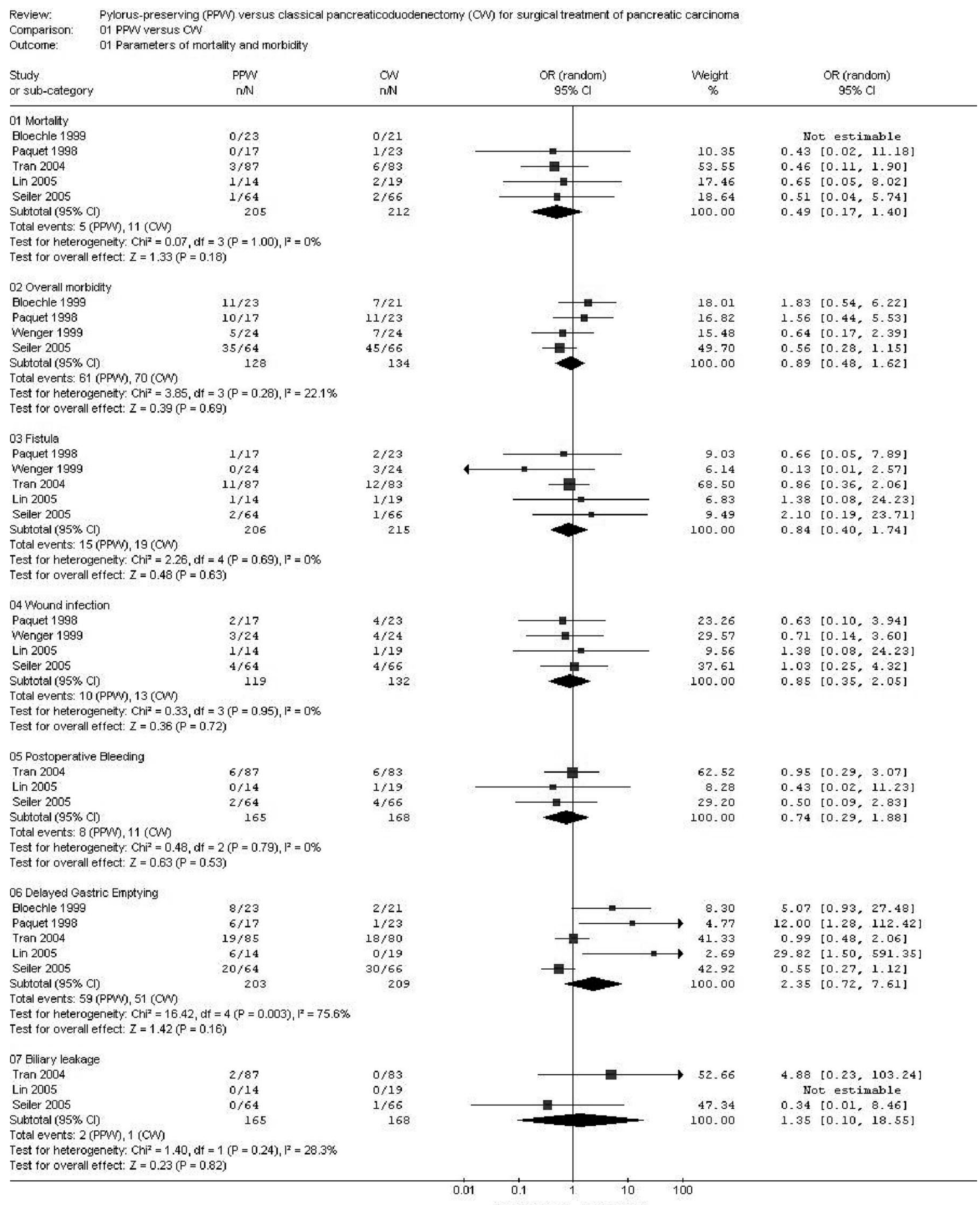

FIGURE 1. (*Continued*).

The summarized effect size of 3 RCTs[32–34] comparing biliary leakage following PPW and CW showed no difference: 2 of 165 (1.2%) in the PPW group versus 1 of 168 (0.5%) in the CW group (OR, 1.35; 95% CI, 0.10 to 18.55; $P = 0.82$; I^2 test, 28.3%). Three studies[32–34] evaluated postoperative bleeding, with 8 of 165 patients (4.8%) in the PPW group and eleven of 168 patients (6.5%) in the CW group, which was statistically nonsignificant (OR, 0.74; 95% CI, 0.29 to 1.88; $P = 0.53$; I^2 test, 0%). Wound infection showed similar levels and occurred in 10 of 119 (8.4%) patients in the PPW group and in 13 of the 132 (9.8%) patients in the CW group (OR, 0.85; 95% CI, 0.35 to 2.05; $P = 0.72$; I^2 test, 0%).

TABLE 3. Critical Appraisal of 6 Studies (578 Patients Randomized/465 Analyzed) Comparing the Pylorus-Preserving Whipple (PPW) and Classical Whipple Procedure (CW)

Study	Study Design; Study Population (group size)	Perioperative Parameters			Outcome Parameters			Critical Appraisal; Level of Evidence†; Grade of Recommendation†
			PPW	CW		PPW n = 14	CW n = 19	Small sample size
Lin et al[32]	RCT; Pancreatic/periampullary cancer	Operation time (min)	221 ± 35	271 ± 65	Mortality	1 (7.1%)	0 (0%)	No description of sample size calculation
	(n = 36) (randomized)	Blood loss (mL)	446 ± 342	1212 ± 194	Morbidity	NA	NA	Inadequate description of randomization process
	PPW n = 14 PP	Blood replacement (units)	1.0 ± 1.4	1.6 ± 2.6	DGE	6 (42.8%)*	0 (0%)	Insufficient definition of outcome parameters
	CW n = 19 PP	Hospital stay (days)	NA	NA	Bleeding	0 (0%)	1 (5.2%)	No description of allocation concealment/ blinding
		Perioperative treatment	NA	NA	Fistula	1 (7.1%)	1 (5.2%)	Follow-up not specified
		Somatostatin application	None	None	Bile leak	0 (0%)	0 (0%)	Short- and long-term results inconsistent
		Erythromycin application	NA	NA	Wound infection	1 (7.1%)	1 (5.2%)	
					Intra-abdominal abscess	0 (0%)	1 (5.2%)	
					Relaparotomy	NA	NA	
						PPW	CW	LoE 1b
					LN+	NA	NA	GoR A
					Radicality (R0)	NA	NA	
					Median survival (mo)	33	12	
					Median follow-up (mo)	NA	NA	
Seiler et al[33]	RCT		PPW	CW		PPW (n = 64)	CW (n = 66)	+ description of sample size calculation
	Pancreatic/periampullary cancer	Operation time (min)	382 (240–645)*	449 (240–780)	Mortality	1 (2%)	2 (3%)	+ reporting in accordance with CONSORT
	n = 240 (randomized)		1198 (400–4000)*		Morbidity	35 (54.7%)	45 (68.2%)	+ proper reporting of sequential randomization
	PPW n = 64 PP	Blood loss (mL)	0.9 (0–6)*	1500 (400–6000)	DGE	20 (31%)	30 (45%)	+ adequate definition of outcome parameters
	CW n = 66 PP		19.7 (10–61)	1.9 (0–10)	Bleeding	2 (3%)	4 (6%)	+ balanced study population
		Blood replacement (units)	Antibiotic prophylaxis	20.8 (8–67)	Fistula	2 (3%)	1 (2%)	+ sequential, personal follow-up
		Hospital stay (days)	100–200 μg 3 × 1 (7 d)	Antibiotic prophylaxis	Bile leak	0 (0%)	1 (1.5%)	Allocation concealment unclear
		Perioperative treatment	None	100–200 μg 3 × 1 (7 d)	Infection (wound or abscess	4 (6%)	4 (6%)	PP analysis (54.1% of randomized patients)

(*Continued*)

TABLE 3. (*Continued*)

Study	Study Design; Study Population (group size)	Perioperative Parameters			Outcome Parameters			Critical Appraisal; Level of Evidence†; Grade of Recommendation†
			PPW	CW		PPW n = 14	CW n = 19	Small sample size
				None	Relaparotomy			No specification of loss to follow-up
		Somatostatin application				NA	NA	
		Erythromycin application						
						PPW (n = 53)	CW (n = 57)	LoE 1b
					LN+	33 (62%)	41 (72%)	GoR A
					Radicality (R0)	48 (91%)	45 (79%)	
					Median survival (mo)	34.0 (20.8–47.2)	27.0 (17.2–36.8)	
					Median follow-up (mo)	63.1 (4–93)	63.1 (4–93)	
Tran et al[34]	RCT		PPW	CW		PPW (n = 87)	CW (n = 83)	+ description of sample size calculation
	Pancreatic/periampullary cancer	Operation time (min)	300 (130–600)	300 (160–480)	Mortality	3 (3%)	6 (7%)	+ adequate reporting of sequential randomization and allocation concealment
	n = 170 (randomized)	Blood loss (mL)	2000 (400–21,000)	2000 (300–9500)	Morbidity	NA	NA	+ adequate definition of outcome parameters
	PPW n = 87 ITT		2	2	DGE	19/85 (22%)	18/80 (23%)	+ balanced study population
	CW n = 83 ITT	Blood replacement (units)	18 (4–175)	20 (11–138)	Bleeding	6 (7%)	6 (7%)	+ multicenter approach
		Hospital stay (days)	Antibiotic prophylaxis, H2-receptor antagonists; drain in operating area	Antibiotic prophylaxis, H2-receptor antagonists	Fistula	11 (13%)	12 (14%)	+ in-house sequential follow-up
		Perioperative treatment	100 μg preoperative + 3 × 1 postoperative	Drain in operating area	Bile leak	2 (2%)	0 (0%)	+ no loss to follow up
			(7 d)	100 μg preoperative + 3 × 1 postoperative	Wound infection	NA	NA	+ ITT analysis
			None	(7 d)	Intra-abdominal abscess	9 (10%)	8 (10%)	Short follow-up period
				None	Relaparotomy	13 (15%)	16 (19%)	

(*Continued*)

TABLE 3. (*Continued*)

Study	Study Design; Study Population (group size)	Perioperative Parameters			Outcome Parameters			Critical Appraisal; Level of Evidence†; Grade of Recommendation†
			PPW	CW		PPW n = 14	CW n = 19	Small sample size
		Somatostatin application						
		Erythromycin application						
						PPW	CW	LoE 1b
					LN+	37/72 (51.4%)	38/69 (55%)	GoR A
					Radicality (R0)	53/72 (73.6%)	57/69 (82.6%)	
					Median survival (mo)	12	11	
					Median follow-up (mo)	18.5 (1–115)	18.5 (1–115)	
Wenger et al[20]	RCT		PPW	CW		PPW n = 24	CW n = 24	+ sequential, personal follow-up
	Pancreatic/periampullary cancer	Operation time (min)	206 ± 48*	306 ± 54	Mortality	NA	NA	Small sample size
	n = 48 (randomized)	Blood loss (mL)	NA	NA	Morbidity	(20.8%)	7 (29.1%)	No description of sample size calculation
	PPW n = 24 PP	Blood replacement (units)	5.5 ± 3.1	6.3 ± 5.2	DGE	NA	NA	Inadequate reporting on randomization process
	CW n = 24 PP	Hospital stay (days)	19.1 ± 11.3	20.9 ± 13.8	Bleeding	NA	NA	No description of allocation concealment/blinding
		Perioperative treatment	NA	NA	Fistula	NA	NA	Only R0 resections included/randomized (selection bias)
					Bile leak	NA	NA	Insufficient definition of outcome parameters
		Somatostatin application	NA	NA	Wound infection	3 (12.5%)	4 (16.6%)	Loss to follow-up 70.8% (PPW) and 58.3% (CW)
		Erythromycin application	NA	NA	Intra-abdominal abscess	NA	NA	
					Relaparotomy	NA	NA	
						PPW	CW	LoE 1b
					LN+	12 (50%)	13 (54%)	GoR A
					Radicality (R0)	4 (100%)	24 (100%)	
					Median survival (mo)	12.5 ± 5.3	11.9 ± 4.2	
					Median follow-up (mo)	NA	NA	
Bloechle et al[35]	RCT		PPW	CW		PPW (n = 23)	CW (n = 21)	Small sample size
	Pancreatic/periampullary cancer	Operation time (min)	239 ± 79*	285 ± 91	Mortality	0%	0%	No description of sample size calculation

(*Continued*)

TABLE 3. (*Continued*)

Study	Study Design; Study Population (group size)	Perioperative Parameters			Outcome Parameters			Critical Appraisal; Level of Evidence†; Grade of Recommendation†
			PPW	CW		PPW n = 14	CW n = 19	Small sample size
	n = 44 (randomized)	Blood loss (mL)	NA	NA	Morbidity	11 (48%)	7 (33%)	No description of randomization process
	PPW n = 23 PP	Blood replacement (units)	NA	NA	DGE	8 (34%)	2 (9%)	No description of allocation concealment/blinding
	CW n = 21 PP	Hospital stay (days)	NA	NA	Bleeding	NA	NA	Insufficient definition of outcome parameters
		Perioperative treatment	NA	NA	Fistula	NA	NA	No specification of follow-up
					Bile leak	NA	NA	
		Somatostatin application	NA	NA	Wound infection	NA	NA	
		Erythromycin application	NA	NA	Intra-abdominal abscess	NA	NA	
					Relaparotomy	NA	NA	
						PPW	CW	LoE 1b
					LN+	NA	NA	GoR A
					Radicality (R0)	NA	NA	
					Median survival (mo)	NA	NA	
					Median follow-up (mo)	18 (12–30)	18 (12–30)	
Paquet et al[36]	RCT		PPW	CW		PPW n = 17	CW n = 23	+ randomization process described
	Pancreatic/periampullary cancer	Operation time (min)	NA	NA	Mortality	0%	1 (4%)	+ sequential, personal, long follow-up period
	n = 40 (randomized)	Blood loss (mL)	NA	NA	Morbidity	10 (59%)	11 (48%)	Small sample size
	PPW n = 17 PP	Blood replacement (units)	NA	NA	DGE	6 (35%)*	1 (4%)	No description of sample size calculation
	CW n = 23 PP	Hospital stay (days)	NA	NA	Bleeding	NA	NA	No description of allocation concealment/ blinding
		Perioperative treatment	NA	NA	Fistula	1 (6%)	2 (9%)	Insufficient definition of outcome parameters
					Bile leak	NA	NA	
		Somatostatin application	NA	NA	Wound infection	NA	NA	
		Erythromycin application	NA	NA	Intra-abdominal abscess	NA	NA	
					Relaparotomy	NA	NA	
						PPW	CW	LoE 1b
					LN+	NA	NA	GoR A
					Radicality (R0)	17 (100%)	23 (100%)	

(*Continued*)

TABLE 3. (*Continued*)

Study	Study Design; Study Population (group size)	Perioperative Parameters		Outcome Parameters			Critical Appraisal; Level of Evidence†; Grade of Recommendation†
		PPW	CW		PPW n = 14	CW n = 19	Small sample size
				Median survival (mo)	NA	NA	
				Median follow-up (mo)	24–144	24–144	

Values are given as mean ± SD where available; values in parentheses are range or percentages.
*$P < 0.05$.
†Level of evidence (LoE) and Grade of Recommendation (GoR) according to the Centre of Evidence Based Medicine, Oxford, UK, http://www.cebm.net/.
NA, not applicable; RCT, randomized controlled trial; ITT, intention-to-treat analysis; PP, per protocol analysis; DGE, delayed gastric emptying; LN+, positive lymph node status; LoE, level of evidence (according to the Centre for Evidence Based Medicine, UK, http://www.cebm.jr2.ox.ac.uk).

The fistula rate also showed no difference between both groups: 15 of 206 patients undergoing a PPW (7.3%) versus 19 of 215 patients in the CW group (8.8%) (OR, 0.84; 95% CI, 0.40 to 1.74; $P = 0.63$; I^2 test, 0%), as shown in the MA of 5 RCTs[20,32–34,36] (Fig. 2).

Survival

Four studies[32–34,36] provided survival data suitable for MA: long-term results (60 months[32,34,36] and 36 months,[33] actuarial Kaplan-Meier analysis) from a total of 284 patients (138 PPW; 146 CW) were evaluated comparing the hazard ratios (HR) and the corresponding 95% CI in the random effects model. As in the findings of the individual trials, the summarized effect size indicated no difference in survival following PPW or CW, respectively (HR, 0.74; 95% CI, 0.52 to 1.07; $P = 0.11$; I^2 test, 31.1%) (Fig. 3).

DISCUSSION

The preservation of the pylorus in patients undergoing duodenopancreatectomy for cancer has been a controversial issue for the last decade. Numerous studies have been performed, including several RCTs, but the cumulative knowledge gained from these studies needed to be captured in a quantitative summary of the results to establish whether the pylorus-preserving pancreaticoduodenectomy (PPW) is a better technique than the classic Whipple (CW).

From a curative perspective, this SR with MA provides further evidence that the CW is not better than the PPW procedure. Pooled long-term results of 4 RCTs showed no difference in terms of overall survival (HR, 0.74; $P = 0.11$). Our findings are in line with a recently published study by Bassi et al[37] where survival data were correlated with the type of surgery by multivariate analysis. The results indicated that neither the type of surgery (PPW vs. CW: HR, 0.80; $P = 0.078$) nor the occurrence of postoperative complications significantly affected the hazard of death, once tumor staging is taken into account (grade, nodal status, and maximum tumor size). As shown by Neoptolemos et al,[38] not the resection margin status R0/R1, but the tumor grade and lymph node status were by far the most powerful prognostic factors of survival.

Mortality and cumulative morbidity are not significantly different between both techniques so that they can be said to be in clinical equipoise. As for surgically and clinically relevant parameters of morbidity, we found in particular no significant differences for the occurrence of pancreatic fistula (OR, 0.84; $P = 0.63$), biliary leakage (OR, 1.35; $P = 0.82$), and postoperative bleeding (OR, 0.74; $P = 0.53$).

Concerning DGE, previous reports of nonrandomized cohort studies[22,39] stating higher rates of DGE in the PPW procedure could not be confirmed by the results of prior RCTs and our MA: Three studies[32,35,36] of the 6 included studies showing higher rates of DGE in the PPW group were also the smallest ones. Given a nonsignificant difference of DGE when considering all included studies (29.1% PPW vs. 24.4% CW: OR, 2.35; $P = 0.16$), this result indicates that underpowered studies potentially overestimate the benefits of CW on DGE.

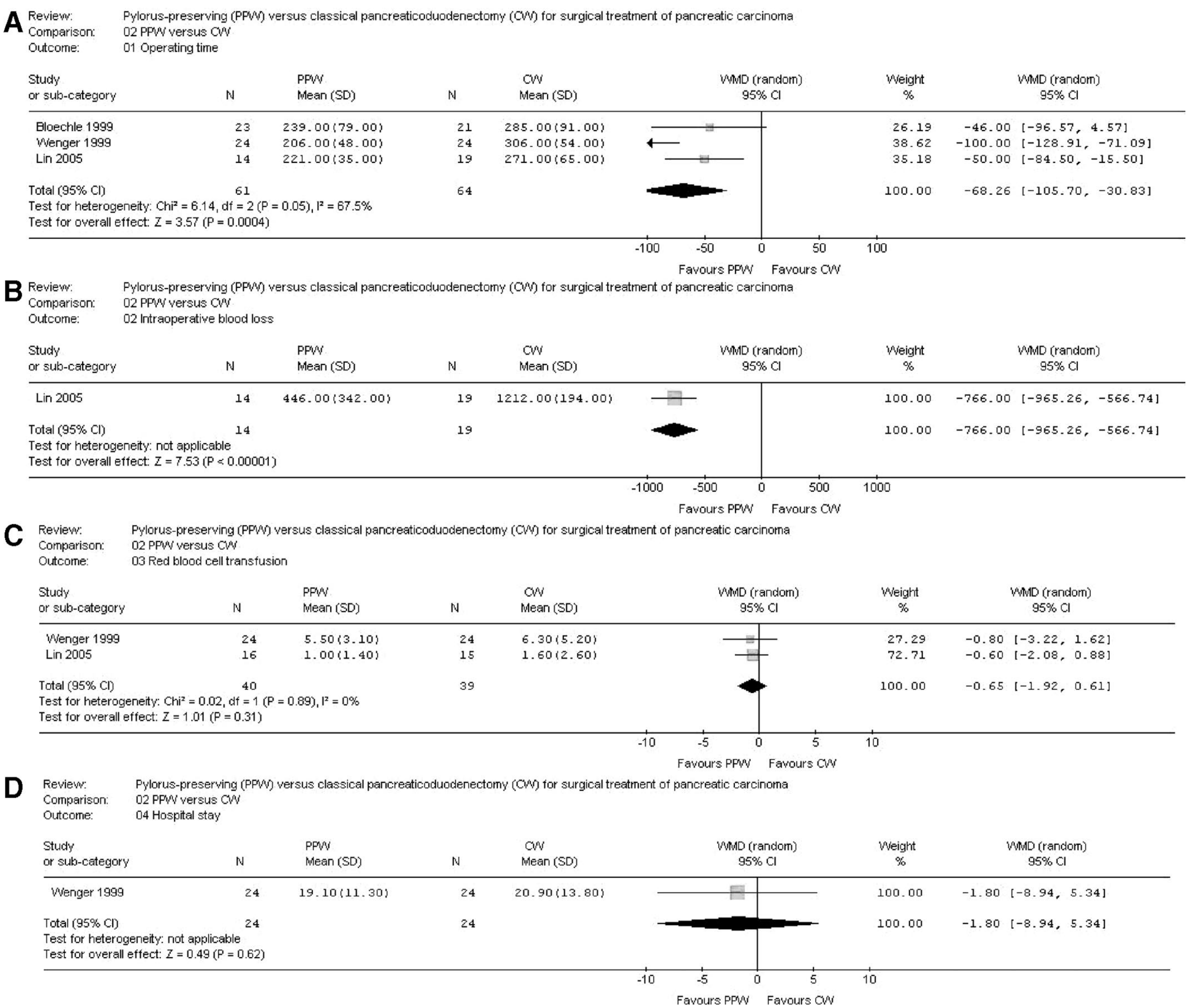

FIGURE 2. Meta-analysis of parameters of mortality and morbidity. Effect estimates (odds ratio; 95% CI). Pooled treatment effect is shown as a diamond that spans the 95% CI. Study quality assessment: allocation concealment adequate (A), unclear (B), inadequate (C), or not used (D).

Our Cochrane highly sensitive search strategy was approved by an expert in the field (G.A.) but, because of incompleteness, may still be biased. In an attempt to identify all relevant studies, we contacted experts in pancreatic surgery and clinical research to identify ongoing trials. However, no additional study has been brought to our knowledge.

Systematic reviews currently provide the best methodology to summarize the existing evidence, but the quality of such reviews depends on the quality of the primary studies.[40,41] In our case, the reviewed studies are partially marred by bias and clinical heterogeneity, which may distort our results.

The fact that the randomization process has been carried out differently in the reviewed studies can be considered as a source of bias, as adequate randomization and allocation concealment generates balanced groups for known, unknown, and unmeasured confounders. Three studies[33,34,36] of the 6 included studies provided adequate description of the randomization process, whereas the 3 other studies[20,32,35] failed to describe the method of allocation satisfactorily.

Moreover, maintained allocation concealment and blinding of the outcome assessor were specified only in 2 trials.[33,34]

Also, median follow-up and follow-up sequences varied significantly between the individual studies (median follow-up, 18[35] months to 144 months[36]). This insufficient reporting on inconsistent follow-up sequences is a possible indicator of performance bias.

Furthermore, we found varying or even lacking definitions of surrogate parameters such as pancreatic fistula and

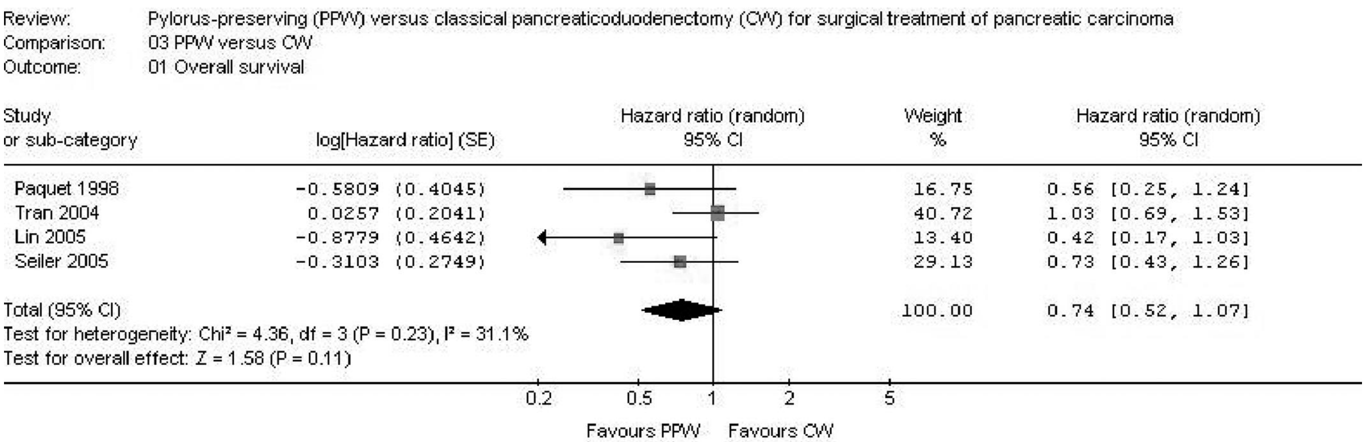

FIGURE 3. Meta-analysis of perioperative factors, length of hospital stay, and overall survival. Effect estimates (odds ratio; 95% CI). Pooled treatment effect is shown as a diamond that spans the 95% CI.

TABLE 4. Pooled Ranges of Mortality, Overall Morbidity, Available Pancreas-Associated Morbidity, and Survival After PPW and CW

	PPW	CW
Mortality	0% (35) to 7.1% (50)	0% (35,50) to 7% (34)
Morbidity	20.8% (20) to 59% (36)	29.1% (20) to 68.2% (33)
DGE	22% (34) to 42.8% (50)	0% (32) to 45 (33)
Fistula	3% (33) to 13% (34)	2% (33) to 14% (34)
Bile leak	0% (32,33) to 2% (34)	0% (32,34) to 1.5% (33)
Median survival (mo)	12 (34) to 34 (33)	11 (34) to 27 (33)

References are in parentheses.

DGE. The trials by Seiler et al[33] and Tran et al[34] provided the most comprehensive definitions. Four trials[20,32,35,36] did not specify the criteria of their endpoints at all. The heterogeneous definition of outcome parameters may have caused detection bias.

At the moment, there are no internationally accepted scaled definitions for surgical outcome parameters in pancreatic cancer surgery. Efforts, such as the consensus conference of the international study group for definition of postoperative pancreatic fistula, should be encouraged to reduce interobserver variability.[42]

Concerning the use of antibiotics, somatostatin, drains, nasogastric tubes, etc, we observed a nonstandardized therapeutic concept or even nonreporting with respect to dosage, route, frequency, and length of administration. Thus, the considerable variation of perioperative management is a further indicator for of interstudy heterogeneity that may influence the external validity of the summarized results.

Another possible source of bias lies in the statistical analysis. Only one trial[34] used the intention-to-treat method, whereas the 5 remaining trials[20,32,33,35,36] applied the PP analysis. This distorted analysis of patients lost to follow-up or missing information on excluded patients (attrition bias) makes it difficult to decide whether the remaining study population is representative (external validity). Moreover, statistical analysis of obviously underpowered trials[32] reduces the explanatory power of these results.

In this context, we should point out that we did not investigate the influence of the neo- and adjuvant treatment, as relevant data were not reported in an interpretable way in the reviewed studies. Therefore, our results may be biased since adjuvant treatment, eg, chemotherapy or chemo-radiation, represents a possible confounder of an impact on survival, mortality and morbidity in a neoadjuvant setting.

The trial by Yeo et al[43,44] had to be excluded from our analyses due to the fact that patients were randomized for pancreaticoduodenectomy with standard versus extended lymphadenectomy and not explicitly for PPW versus CW. Although 86% of patients of the "standard" group were subjected to a PPW and all of the radical (extended) group underwent a classic Whipple procedure with retroperitoneal lymphadenectomy, inclusion of these 294 patients might have contorted the results.

Despite the mentioned sources of clinical and methodologic heterogeneity, we still observed adequate balanced groups when we compared interstudy baseline population characteristics: all analyzed patients were included due to suspect pancreatic or periampullary carcinoma. Our SR also revealed a balanced distribution of R0/R1 resections (mean R0 resection, 91.1% [PPW]; 90.4% [CW]) and lymph node status (mean positive lymph node status, 54.4% [PPW]; 60.3% [CW]). The calculated average level of the statistical heterogeneity of all 12 meta-analytic approaches indicated moderate heterogeneity of 22.4% (I^2 test). Nevertheless, given obvious sources of clinical and methodologic heterogeneity, we decided to compute the statistics of our MA using the random effects model, which allows for variation in the treatment effects of the individual studies but also provides a more conservative pooled effect estimate.[30] Because of multifactorial heterogeneity and only 6 trials included, subgroup analysis seemed not to be feasible.

CONCLUSION

Given these obvious sources of bias (small sample size, lacking definition of outcome parameters, inexplicit randomization, and allocation concealment), the results of our systematic review and meta-analysis should be interpreted with caution. We must recognize that neither PPW nor CW has been showed to be the better technique. To demonstrate a clear superiority of the PPW technique, much larger and rigorously designed studies would be needed than currently available. On the other hand, the present study illustrates an intolerable situation. Six trials of the highest level of evidence addressing the same surgical problem still show major clinically relevant heterogeneity. This highlights the urgent need for the surgical community to develop standardized RCTs for complex interventions. To reach an evidence-based consensus on refined definitions of surgical interventions and their possible outcome parameters, international cooperation is called upon. This systematic review and meta-analysis might serve as a basis for such a development.

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