Meta-analysis

Systematic review and meta-analysis of outcomes after intraoperative pancreatic duct stent placement during pancreaticoduodenectomy

J. J. Xiong[1], K. Altaf[3], R. Mukherjee[3], W. Huang[2,3], W. M. Hu[1], A. Li[1], N. W. Ke[1] and X. B. Liu[1]

[1]Department of Hepato-Biliary-Pancreatic Surgery and [2]Pancreatic Diseases Research Group, Department of Integrated Traditional and Western Medicine, West China Hospital, Sichuan University, Chengdu, China, and [3]Liverpool National Institute for Health Research Pancreas Biomedical Research Unit, Royal Liverpool University Hospital, Liverpool, UK

Correspondence to: Professor X. B. Liu, Department of Hepato-Biliary-Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu 610041, China (e-mail: liuxb2011@126.com)

Background: **Postoperative pancreatic leakage after pancreaticoduodenectomy is often serious. Although some studies have suggested that stenting the anastomosis can reduce the incidence of this complication, the value of stenting in the setting of pancreaticoduodenectomy remains unclear.**

Methods: **Studies comparing outcomes of stent *versus* no stent, and internal *versus* external stent placement for pancreaticoduodenectomy were eligible for inclusion. Pooled odds ratios (ORs) with 95 per cent confidence intervals were calculated using fixed- or random-effects models.**

Results: **From a search of the literature published between January 1973 and September 2011, five randomized clinical trials (RCTs) and 11 non-randomized observational clinical studies (OCS) involving 1726 patients were selected for inclusion in this review. Meta-analysis of RCTs revealed that placing a stent in the pancreatic duct did not reduce the incidence of postoperative pancreatic fistula. External stents had no advantage over internal stents in terms of clinical outcome. Subgroup analyses revealed that use of an external stent significantly reduced the incidence of pancreatic fistula (RCTs: OR 0·42, 0·24 to 0·76, $P = 0·004$; OCS: OR 0·43, 0·27 to 0·68, $P < 0·001$), delayed gastric emptying (RCTs: OR 0·41, 0·19 to 0·87, $P = 0·02$) and postoperative morbidity (RCTs: OR 0·55, 0·34 to 0·89, $P = 0·02$) compared with no stent.**

Conclusion: **Pancreatic duct stenting did not reduce the incidence of pancreatic fistula and other complications in pancreaticoduodenectomy compared with no stenting. Although no difference was found between external and internal stents in terms of efficacy, external stents seemed to reduce the incidence of pancreatic fistula compared with control.**

Paper accepted 27 March 2012

Published online 24 May 2012 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.8788

Introduction

Pancreaticoduodenectomy (PD) is the standard resection for various benign and malignant diseases of the periampullary region[1,2]. It is a complex surgical procedure historically associated with high operative mortality rates, although technical advances and centralization of care have improved the safety of PD significantly in many institutions around the world[3–5]. High-volume centres typically achieve operative mortality rates below 5 per cent[2,6]. Surgical morbidity, nevertheless, remains high, with 30–40 per cent of patients experiencing one or more complications[4,7]. Pancreatic fistula (PF), intra-abdominal abscesses and delayed gastric emptying (DGE) are all reported frequently. PF is the most common major complication after PD, with a frequency ranging from 2 to 20 per cent[8], and is associated with increased morbidity and mortality[9]. A number of techniques have been proposed to reduce PF following PD. These include the use of the somatostatin analogue octreotide[10,11], reinforcement of the pancreaticoenteric anastomosis with fibrin glue[12], placement of a pancreatic duct stent[13,14] and reconstruction with a pancreaticogastrostomy[15]. Results are often discordant, and definitive evidence regarding the ideal management and optimal surgical technique to reduce the postoperative PF rate is not yet available[16].

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

The placement of a stent through the pancreatic anastomosis is an attractive strategy to reduce the incidence of PF, with some authors suggesting potential advantages in terms of reduced PF and overall mortality rates[13,14,17], although other studies reported no effect[18–20]. One study suggested that stent placement led to higher PF and morbidity rates compared with anastomosis without a stent[21].

On the basis of these mixed findings, the primary objective of this systematic review was to meta-analyse the evidence regarding outcomes of PD with and without stenting, and to determine whether there was a difference between use of internal *versus* external stents.

Methods

Study selection

A computerized search in MEDLINE (PubMed), Embase, the Cochrane Library and the Cochrane Clinical Trials Registry was performed to identify human trials published in the English literature of peer-reviewed medical journals between January 1973 (when intraoperative pancreatic duct stent placement in PD was first mentioned) to September 2011. For this purpose, medical subject heading (MeSH) terms used were: 'pancreaticoduodenectomy', 'stent', 'pancreaticojejunostomy', 'pancreaticogastrostomy', 'pancreatic anastomosis', 'anastomotic leak' and 'pancreatic fistula'. Equivalent free-text search terms were used in the search strategy. Relevant papers were also identified from the bibliographies of papers obtained through the search. All searches were performed by two independent researchers. 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; when this failed, a third author adjudicated.

Inclusion and exclusion criteria

Two authors identified and screened the search findings for potentially eligible randomized clinical trials (RCTs) and observational clinical studies (OCS) that compared either pancreatic duct stent with no stent, or internal stent with external stent placement in patients undergoing PD. Studies comparing external or internal stent with no stents were also examined in detail.

For inclusion in the meta-analysis, a study had to fulfil the following criteria: an English language article published in a peer-reviewed journal, with the report describing at least one of the outcomes mentioned. When studies were reported by the same institution, either the study of better quality or the more recent publication was included.

The following were excluded: abstracts, letters, editorials, expert opinions, reviews without original data and case reports, studies with duodenum-preserving pancreatic head resection or total pancreatectomy, and studies lacking a control group.

Definitions of complications

The primary outcome measure was the incidence of PF, as defined by the Johns Hopkins Hospital[18]

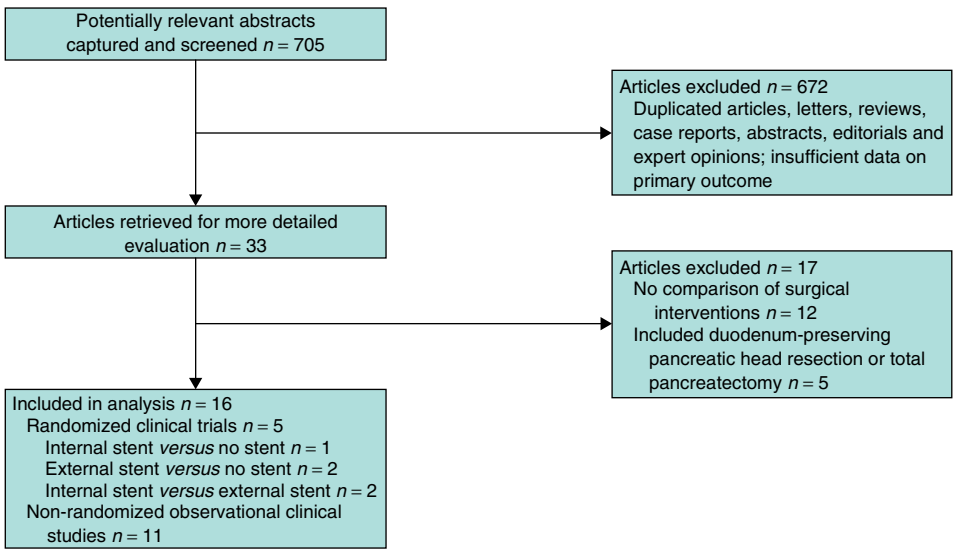


Fig. 1 Study flow chart

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

and the International Study Group on Pancreatic Fistula (ISGPF)[8]. Secondary outcome measures included DGE, postoperative intra-abdominal collection, overall morbidity and mortality. DGE was defined as the need for nasogastric decompression beyond 9 or 10 days after surgery, or inability to return to a standard diet by the end of the first week. Postoperative intra-abdominal collection was defined by the presence of radiological evidence. Postoperative morbidity was defined as total complications from date of operation to discharge, whereas overall mortality was represented as the number of patients who died from any cause, directly or indirectly related to PD, before discharge.

Data collection

Data were extracted independently from every study by two reviewers, applying a standard review form,

Table 1 Characteristics of included studies

Reference	Country	Years of study	Design	Stents compared	No. of patients	Stent type			O or S	Score*
						Int	Ext	None		
Matsusue *et al*.[50]	Japan	1981–1996	PNR	Ext or Int *versus* none	100	30	17	53	–	3
Roder *et al*.[17]	Germany	1994–1997	PNR	Ext *versus* none	85	–	44	41	Yes	3
Ohwada *et al*.[49]	Japan	1997–2000	Retro	Ext *versus* Int	74	37	37	–	No	1
Tani *et al*.[51]	Japan	1994–2002	Retro	Ext *versus* none	76	–	31	45	–	1
Imaizumi *et al*.[19]	Japan	1992–2003	Retro	Int and Ext *versus* none	168	–	–	123	–	1
Winter *et al*.[18]	USA	2004–2005	RCT	Int *versus* none	234	115	–	119	No	3
Poon *et al*.[13]	Hong Kong	2000–2006	RCT	Ext *versus* none	120	–	60	60	No	3
Choe *et al*.[52]	South Korea	1996–2006	Retro	Ext *versus* none	172	–	58	114	Yes	1
Sriussadaporn *et al*.[46]	Thailand	1991–2007	Retro	Ext *versus* none	73	–	45	28	No	1
Hakamada *et al*.[47]	Japan	2003–2006	Retro	Ext *versus* none	63	–	35	28	–	1
Kamoda *et al*.[44]	Japan	2003–2007	RCT	Ext *versus* Int	43	21	22	–	No	2
Satoi *et al*.[9]	Japan	2004–2008	Retro	Ext *versus* none	129	–	51	78	No	1
Smyrniotis *et al*.[20]	Greece	2000–2008	PNR	Int *versus* none	82	41	–	41	No	3
Tani *et al*.[45]	Japan	2005–2007	RCT	Ext *versus* Int	100	50	50	–	No	3
Lai *et al*.[48]	Hong Kong	1999–2008	Retro	Int *versus* none	49	24	–	25	Yes	1
Pessaux *et al*.[14]	France	2006–2009	RCT	Ext *versus* none	158	–	77	81	Yes	3

*Randomized clinical trials (RCTs) were scored according to the Jadad scoring system; the method of McKay and colleagues was used for non-randomized studies. Int, internal stent; Ext, external stent; O, octreotide; S, somatostatin; PNR, prospective non-randomized observational study; Retro, retrospective observational study.

Table 2 Surgical anastomosis technique and definition of pancreatic fistula

Reference	Anastomosis technique	Definition of pancreatic fistula
Matsusue *et al*.[50]	ES (MM)-PJ	> 50 ml/day amylase-rich (> 1000 units) for over 1 week
Roder *et al*.[17]	EE (IN)-PJ or ES-PJ or ES (DM)-PJ	> 50 ml/day amylase rich (3 times serum level) after surgery
Ohwada *et al*.[49]	ES (DM)-PJ	> 3 times serum amylase in drainage fluid
Tani *et al*.[51]	ES-PJ or ES (DM)-PJ	> 50 ml/day amylase-rich (3 times serum level) on day 7 or more after surgery
Imaizumi *et al*.[19]	ES (DM)-PJ	Not defined
Winter *et al*.[18]	EE (IN)-PJ or ES (DM)-PJ	ISGPF definition[8] and JHH definition[18]
Poon *et al*.[13]	ES (DM)-PJ	> 10 ml/day (3 times serum level) more than 3 days after surgery
Choe *et al*.[52]	DM-PJ or EE (IN)-PJ	> 50 ml/day amylase-rich (3 times serum level) on day 7 or more after surgery
Sriussadaporn *et al*.[46]	EE-PJ or ES-PJ	ISGPF definition[8]
Hakamada *et al*.[47]	ES (DM)-PJ	Four definitions (including ISGPF[8] and JHH[18])
Kamoda *et al*.[44]	EE (IN)-PJ or ES (DM)-PJ	ISGPF[8] or JHH[18] definition
Satoi *et al*.[9]	ES (DM)-PJ	ISGPF definition[8]
Smyrniotis *et al*.[20]	ES (DM)-PJ	ISGPF definition[8]
Tani *et al*.[45]	ES (DM)-PJ	ISGPF definition[8]
Lai *et al*.[48]	ES (DM)-PJ	ISGPF definition[8]
Pessaux *et al*.[14]	ES (DM)-PG or ES (DM)-PJ	ISGPF definition[8]

ES, end-to-side; MM, mucosa-to-mucosa; PJ, pancreaticojejunostomy; EE, end-to-end; IN, invagination; DM, duct-to-mucosa; ISGPF, International Study Group on Pancreatic Fistula; JHH, Johns Hopkins Hospital; PG, pancreaticogastrostomy.

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

and cross-checked. Inconsistencies were resolved through discussion until consensus was reached, or a third reviewer would take part in the discussion. Qualitative assessment of RCTs was based on the Jadad scoring system[22], taking into consideration the randomization and double-blinding process, and the description of withdrawals or dropouts. Note was also made of the sample size calculation, sequence generation, allocation concealment and definitions of outcome parameters. Observational studies were assessed as described by McKay and colleagues[23], including assessment of data collection (prospective *versus* retrospective), assignment to stent group or no-stent group by means other than the surgeon's preference, and an explicit definition of PF or leak (studies were given a score of 1 for each of these areas, giving a total score of 1–4).

Quantitative data extracted from the selected studies included: population characteristics, intraoperative conditions and outcome parameters (PF, DGE, intra-abdominal collection, postoperative morbidity and overall mortality) in each study.

Statistical analysis

Data analyses were performed using Review Manager 5 software (The Cochrane Collaboration, Oxford, UK). Heterogeneity was evaluated by means of the χ^2 test, with $P < 0{\cdot}100$ considered to represent a significant difference. 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[24]. Initially a fixed-effects model was used to synthesize all data. However, if there was evidence of heterogeneity among the included studies, random-effects analysis according to DerSimonian and

Table 3 Summary of the results on the efficacy of stent insertion after pancreaticoduodenectomy

	No. of studies	No. of patients	Odds ratio	*P*	*P* for heterogeneity	I^2 (%)
Stent *versus* no stent (RCTs)						
Pancreatic fistula	3[13,14,18]	512	0·73 (0·49, 1·10)	0·13	0·02	73
Postoperative morbidity	3[13,14,18]	512	0·72 (0·50, 1·02)	0·07	0·16	45
Overall mortality	3[13,14,18]	512	0·61 (0·22, 1·70)	0·35	0·68	0
Delayed gastric emptying	3[13,14,18]	512	0·67 (0·40, 1·12)	0·13	0·02	76
Intra-abdominal collection	2[13,14]	278	0·74 (0·29, 1·89)	0·52	0·33	0
Stent *versus* no stent (OCS)						
Pancreatic fistula	9[9,17,20,46–48,50–52]	829	0·47 (0·31, 0·72)	< 0·001	0·11	39
Postoperative morbidity	6[9,19,20,46–48]	564	0·82 (0·57, 1·18)	0·28	0·63	0
Overall mortality	8[9,17,19,20,46–48,51]	725	0·65 (0·21, 2·00)	0·45	0·44	0
Delayed gastric emptying	6[9,17,20,46–48]	481	0·80 (0·40, 1·61)	0·53	0·53	0
Intra-abdominal collection	3[20,46,48]	204	2·15 (0·54, 8·51)	0·28	0·62	0
External stent *versus* internal stent (RCTs)						
Pancreatic fistula	2[44,45]	143	0·89 (0·42, 1·87)	0·75	0·44	0
Overall mortality	2[44,45]	143	3·06 (0·12, 76·95)	0·50	–	–
Delayed gastric emptying	2[44,45]	143	1·23 (0·36, 4·24)	0·74	0·59	0
External stent *versus* internal stent (OCS)						
Pancreatic fistula	2[49,50]	121	1·69 (0·33, 8·66)	0·53	0·38	0
External stent *versus* no stent (RCTs)						
Pancreatic fistula	2[13,14]	278	0·42 (0·24, 0·76)	0·004	0·45	0
Postoperative morbidity	2[13,14]	278	0·55 (0·34, 0·89)	0·02	0·30	8
Overall mortality	2[13,14]	278	0·68 (0·19, 2·45)	0·55	0·41	0
Delayed gastric emptying	2[13,14]	278	0·41 (0·19, 0·87)	0·02	0·02	80
Intra-abdominal collection	2[13,14]	278	0·74 (0·29, 1·89)	0·52	0·33	0
External stent *versus* no stent (OCS)						
Pancreatic fistula	7[9,17,46,47,50–52]	668	0·43 (0·27, 0·68)	< 0·001	0·07	48
Postoperative morbidity	3[9,46,47]	265	0·70 (0·43, 1·15)	0·16	0·36	2
Overall mortality	5[9,17,46,47,51]	426	0·30 (0·06, 1·44)	0·13	0·83	0
Delayed gastric emptying	4[9,17,46,47]	350	0·65 (0·28,1·53)	0·32	0·48	0
Internal stent *versus* no stent (OCS)						
Pancreatic fistula	3[20,48,50]	214	1·00 (0·32, 3·09)	0·99	0·66	0
Postoperative morbidity	2[20,48]	131	1·19 (0·57, 2·47)	0·65	0·88	0
Overall mortality	2[20,48]	131	1·04 (0·06, 17·69)	0·98	–	–
Delayed gastric emptying	2[20,48]	131	1·25 (0·36, 4·31)	0·72	0·34	0
Intra-abdominal collection	2[20,48]	131	2·73 (0·51, 14·59)	0·24	0·39	0

Values in parentheses are 95 per cent confidence intervals. RCT, randomized clinical trial; OCS, observational clinical studies.

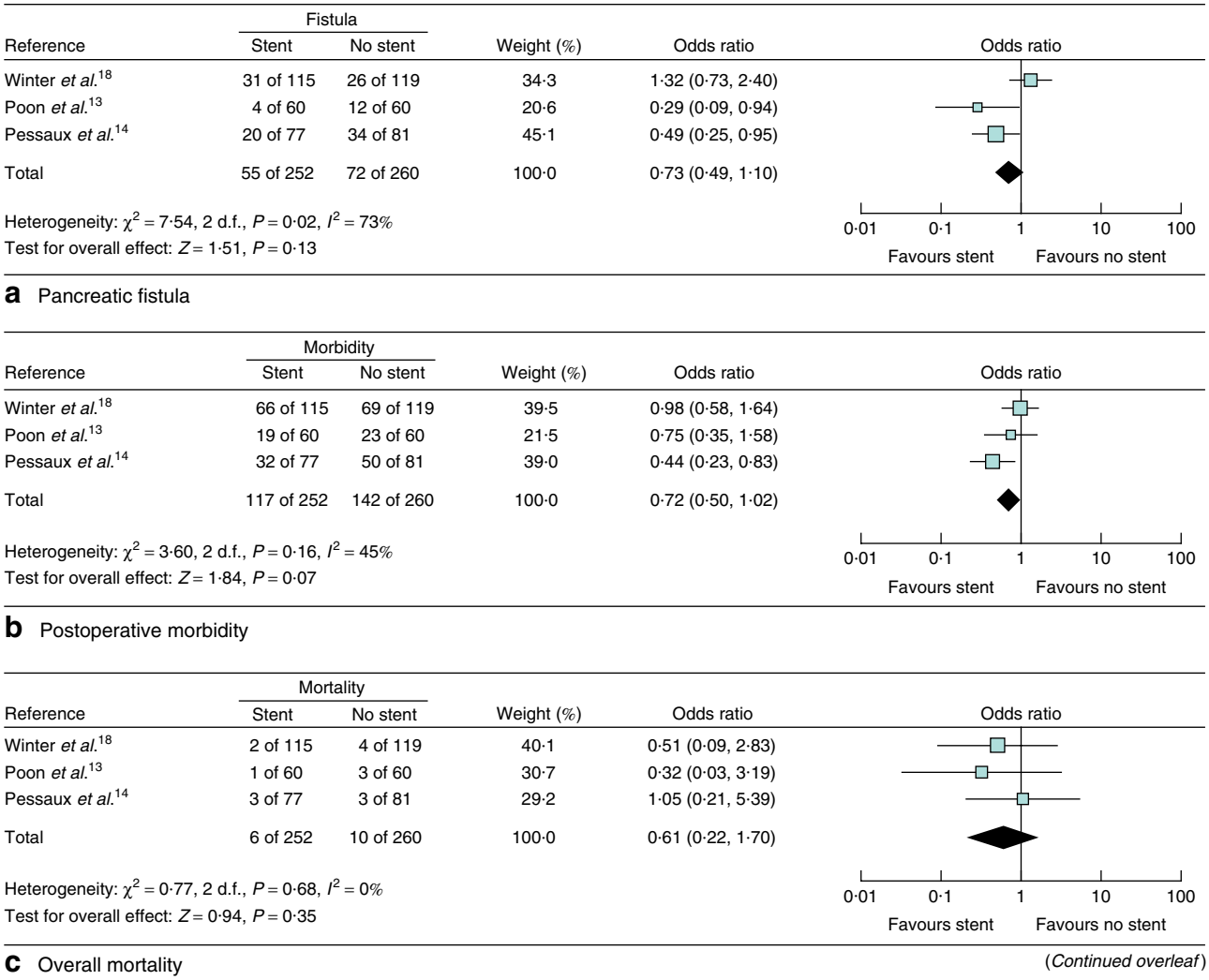
© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

Laird[25] was used. If there was no difference between the results of these models, results for the fixed-effects model were reported. Otherwise, the results of both the fixed-effects and random-effects models were reported. A random-effects model generates a more conservative estimate than an analysis using a fixed-effects model in the absence of clinical heterogeneity[26]. Clinical heterogeneity could be explained by different definitions of outcome parameters, and variability of interventions and perioperative management. Results of all meta-analyses are presented as odds ratios (ORs) with 95 per cent confidence intervals (c.i.).

Data analysis was performed by comparing pancreatic duct stent (external and internal) *versus* no stent, external stent *versus* internal stent, external stent *versus* no stent, and internal stent *versus* no stent. Analyses were run separately for RCTs and OCS. Funnel plots were constructed to evaluate potential publication bias[27], based on the complication PF.

Results

The results of the literature search are shown in *Fig. 1*.



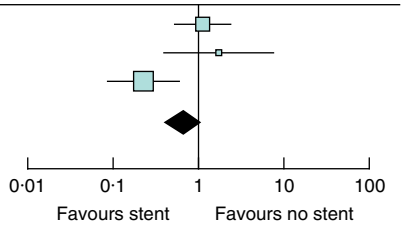
(*Continued overleaf*)

Fig. 2 Meta-analysis for aggregated data in randomized clinical trials comparing effect of stent and no stent on **a** pancreatic fistula rate, **b** postoperative complication rate, **c** overall mortality rate, **d** delayed gastric emptying rate and **e** intra-abdominal collection rate in patients undergoing pancreaticoduodenectomy. Pooled odds ratios with 95 per cent confidence intervals were calculated using the fixed-effects model

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

Reference	Delayed gastric emptying: Stent	Delayed gastric emptying: No stent	Weight (%)	Odds ratio
Winter *et al.*[18]	16 of 115	15 of 119	36·0	1·12 (0·53, 2·39)
Poon *et al.*[13]	5 of 60	3 of 60	7·8	1·73 (0·39, 7·58)
Pessaux *et al.*[14]	6 of 77	22 of 81	56·1	0·23 (0·09, 0·60)
Total	27 of 252	40 of 260	100·0	0·67 (0·40, 1·12)

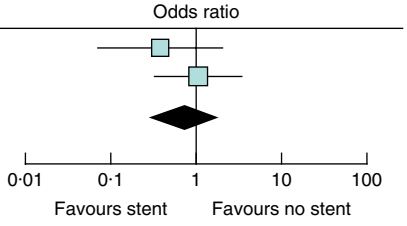
Heterogeneity: $\chi^2 = 8{\cdot}19$, 2 d.f., $P = 0{\cdot}02$, $I^2 = 76\%$
Test for overall effect: $Z = 1{\cdot}53$, $P = 0{\cdot}13$



d Delayed gastric emptying

Reference	Intra-abdominal collection: Stent	Intra-abdominal collection: No stent	Weight (%)	Odds ratio
Poon *et al.*[13]	2 of 60	5 of 60	47·3	0·38 (0·07, 2·04)
Pessaux *et al.*[14]	6 of 77	6 of 81	52·7	1·06 (0·33, 3·43)
Total	8 of 137	11 of 141	100·0	0·74 (0·29, 1·89)

Heterogeneity: $\chi^2 = 0{\cdot}96$, 1 d.f., $P = 0{\cdot}33$, $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}64$, $P = 0{\cdot}52$



e Intra-abdominal collection

Fig. 2 (Continued)

Description of trials included in the meta-analysis

Initially, 33 articles were identified. Of these, 17 were excluded because there was no comparison of surgical interventions[28–39] or studies were related to duodenum-preserving pancreatic head resection or total pancreatectomy[21,40–43]. Of 16 articles identified for inclusion, five were RCTs[13,14,18,44,45] and 11 OCS[9,17,19,20,46–52]. The number of patients in each study ranged from a minimum of 43 to a maximum of 234 (*Table 1*). The surgical anastomosis technique and definition of PF are shown in *Table 2*. Because of variation in the use of perioperative octreotide, the ways in which the surgery was performed and definitions of PF, included studies were analysed separately to determine potential different treatment effects in the groups created for the present study. The results are summarized in *Table 3*.

Stent *versus* no stent

Randomized trials

Three RCTs compared stent with no stent[13,14,18]. All had a clear description of the sample size calculation and intraoperative randomization. No trial was double-blinded, although Poon and co-workers[13] described blinding of the nursing staff who collected the data. Detailed results are presented in *Fig. 2*.

Meta-analysis revealed that 55 (21·8 per cent) of 252 patients in the stent group and 72 (27·7 per cent) of 260 in the no-stent group developed PF (OR 0·73, 95 per cent c.i. 0·49 to 1·10; $P = 0{\cdot}13$). As Winter and colleagues[18] used two definitions of PF, the analysis was performed using both definitions separately. The results were similar and so the ISGPF definition was used for the final analysis, as this was the standard definition in most of the other selected studies. Although some degree of heterogeneity was present among these studies ($I^2 = 73$ per cent), use of the random-effects model did not change the result.

The use of a stent was not associated with a significant reduction in mortality (OR 0·61, 0·22 to 1·70; $P = 0{\cdot}35$), morbidity (OR 0·72, 0·50 to 1·02; $P = 0{\cdot}07$), DGE (OR 0·67, 0·40 to 1·12; $P = 0{\cdot}13$) or intra-abdominal fluid collection (OR 0·74, 0·29 to 1·89; $P = 0{\cdot}52$). Although there was heterogeneity between studies ($I^2 = 76$ per cent) in terms of DGE, no difference was found when a random-effects model was used.

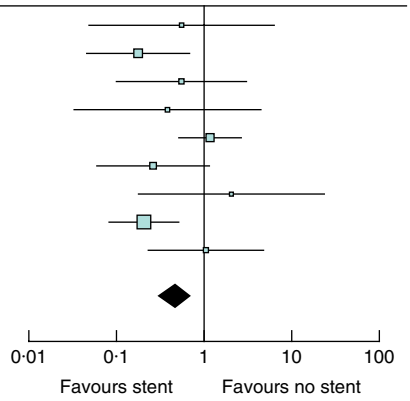
Observational studies

Ten OCS compared stent with no stent[9,17,19,20,46–48,50–52]. Detailed results are presented in *Fig. 3*. One study did not provide a definition of PF but did provide data on postoperative morbidity and overall mortality[19], and was therefore included in the assessment of these outcomes. Another study assessed the incidence of PF using four

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

Reference	Fistula: Stent	Fistula: No stent	Weight (%)	Odds ratio
Matsusue *et al.*[50]	1 of 47	2 of 53	2·9	0·55 (0·05, 6·32)
Roder *et al.*[17]	3 of 44	12 of 41	18·1	0·18 (0·05, 0·68)
Tani *et al.*[51]	2 of 31	5 of 45	6·0	0·55 (0·10, 3·04)
Hakamada *et al.*[47]	1 of 35	2 of 28	3·4	0·38 (0·03, 4·45)
Choe *et al.*[52]	11 of 58	19 of 114	16·2	1·17 (0·52, 2·66)
Sriussadaporn *et al.*[46]	3 of 45	6 of 28	10·8	0·26 (0·06, 1·15)
Smyrniotis *et al.*[20]	2 of 41	1 of 41	1·5	2·05 (0·18, 23·55)
Satoi *et al.*[9]	7 of 51	34 of 78	36·2	0·21 (0·08, 0·51)
Lai *et al.*[48]	4 of 24	4 of 25	5·1	1·05 (0·23, 4·78)
Total	34 of 376	85 of 453	100·0	0·47 (0·31, 0·72)

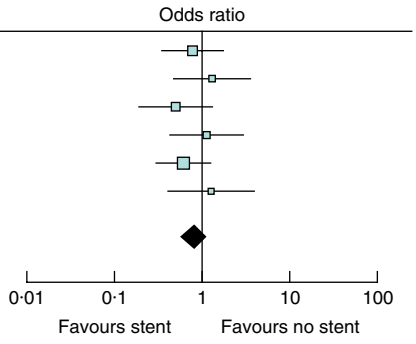
Heterogeneity: $\chi^2 = 13{\cdot}05$, 8 d.f., $P = 0{\cdot}11$, $I^2 = 39\%$
Test for overall effect: $Z = 3{\cdot}44$, $P < 0{\cdot}001$



a Pancreatic fistula

Reference	Morbidity: Stent	Morbidity: No stent	Weight (%)	Odds ratio
Imaizumi *et al.*[19]	10 of 45	33 of 123	21·4	0·78 (0·35, 1·75)
Hakamada *et al.*[47]	16 of 35	11 of 28	10·3	1·30 (0·47, 3·57)
Sriussadaporn *et al.*[46]	15 of 45	14 of 28	17·9	0·50 (0·19, 1·31)
Smyrniotis *et al.*[20]	12 of 41	11 of 41	12·1	1·13 (0·43, 2·96)
Satoi *et al.*[9]	20 of 51	40 of 78	29·9	0·61 (0·30, 1·25)
Lai *et al.*[48]	11 of 24	10 of 25	8·3	1·27 (0·41, 3·94)
Total	84 of 241	119 of 323	100·0	0·82 (0·57, 1·18)

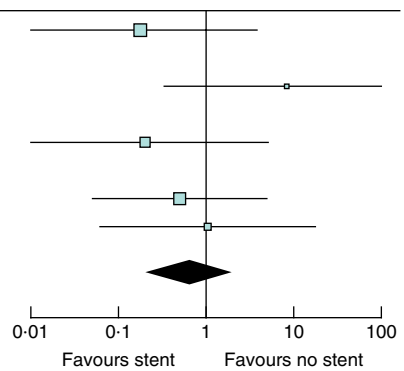
Heterogeneity: $\chi^2 = 3{\cdot}45$, 5 d.f., $P = 0{\cdot}63$, $I^2 = 0\%$
Test for overall effect: $Z = 1{\cdot}09$, $P = 0{\cdot}28$



b Postoperative morbidity

Reference	Mortality: Stent	Mortality: No stent	Weight (%)	Odds ratio
Roder *et al.*[17]	0 of 44	2 of 41	32·4	0·18 (0·01, 3·81)
Tani *et al.*[51]	0 of 31	0 of 45		Not estimable
Imaizumi *et al.*[19]	1 of 45	0 of 123	3·3	8·33 (0·33, 208·15)
Hakamada *et al.*[47]	0 of 35	0 of 28		Not estimable
Sriussadaporn *et al.*[46]	0 of 45	1 of 28	23·0	0·20 (0·01, 5·12)
Smyrniotis *et al.*[20]	0 of 41	0 of 41		Not estimable
Satoi *et al.*[9]	1 of 51	3 of 78	29·4	0·50 (0·05, 4·94)
Lai *et al.*[48]	1 of 24	1 of 25	11·9	1·04 (0·06, 17·69)
Total	3 of 316	7 of 409	100·0	0·65 (0·21, 2·00)

Heterogeneity: $\chi^2 = 3{\cdot}76$, 4 d.f., $P = 0{\cdot}44$, $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}75$, $P = 0{\cdot}45$

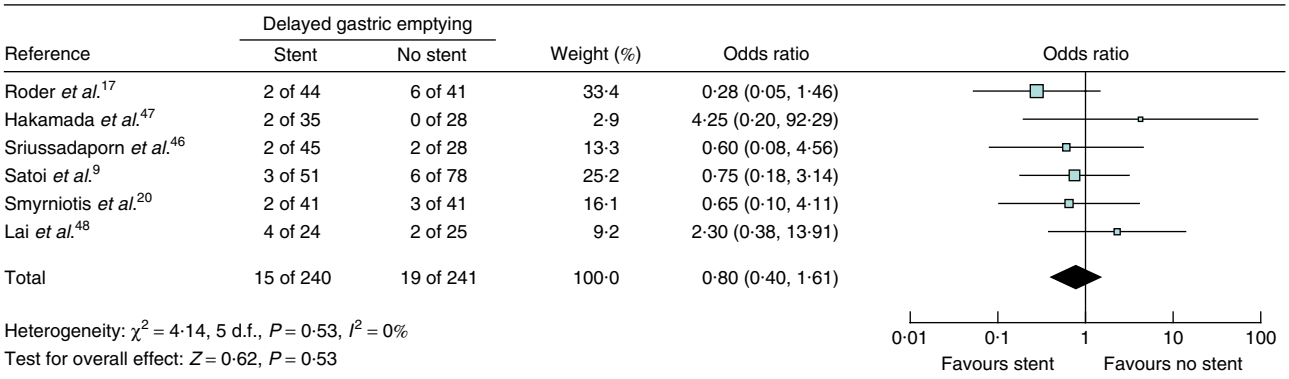


c Overall mortality

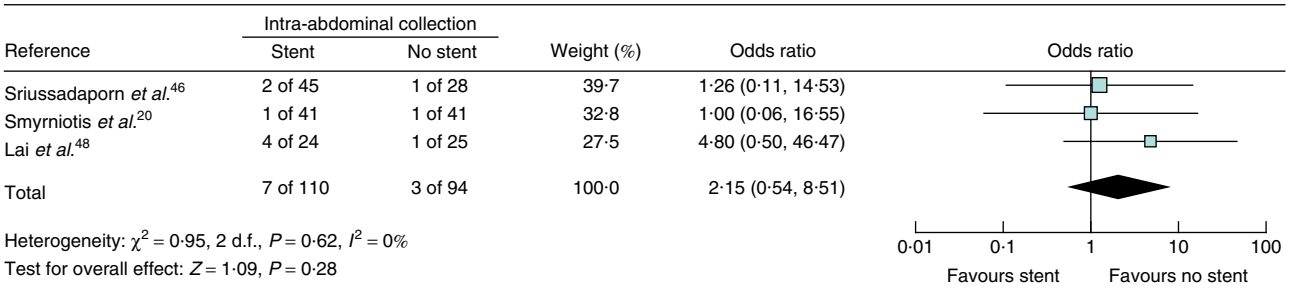
(*Continued overleaf*)

Fig. 3 Meta-analysis for aggregated data in observational clinical studies comparing the effect of stent and no stent on **a** pancreatic fistula rate, **b** postoperative complication rate, **c** overall mortality rate, **d** delayed gastric emptying rate and **e** intra-abdominal collection rate in patients undergoing pancreaticoduodenectomy. Pooled odds ratios with 95 per cent confidence intervals were calculated using the fixed-effects model

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd



d Delayed gastric emptying



e Intra-abdominal collection

Fig. 3 (Continued)

definitions[47] and the results were therefore analysed using each definition separately; finally, the first definition (drainage of more than 50 ml per day of fluid with an amylase content above 3 times the serum amylase activity on day 10 or more after surgery) was used in the final analysis.

Some 9·0 per cent of patients in the stent group and 18·8 per cent in the no-stent group developed PF (OR 0·47, 0·31 to 0·72; $P < 0·001$). There was no significant difference in overall postoperative morbidity (OR 0·82, 0·57 to 1·18; $P = 0·28$) or overall mortality (OR 0·65, 0·21 to 2·00; $P = 0·45$) between the two groups. Neither DGE (OR 0·80, 0·40 to 1·61; $P = 0·53$) nor the incidence of intra-abdominal fluid collection (OR 2·15, 0·54 to 8·51; $P = 0·28$) was affected by stent insertion.

External stent *versus* internal stent

Only four studies (2 RCTs, 2 OCS) examined this issue[44,45,49,50]. The results are shown in *Table 3* with a sensitivity analysis. The rates of PF, DGE and overall mortality were no different between the external and internal stent groups when RCTs and OCS were analysed separately.

External stent *versus* no stent

Randomized trials

Analysis of two RCTs[13,14] revealed that use of an external stent was associated with a statistically significant reduction in the incidence of PF (OR 0·42, 0·24 to 0·76; $P = 0·004$), DGE (OR 0·41, 0·19 to 0·87; $P = 0·02$) and postoperative morbidity (OR 0·55, 0·34 to 0·89; $P = 0·02$). There was no significant difference in overall mortality or development of intra-abdominal collection between the two groups.

Observational studies

Analysis of seven OCS[9,17,46,47,50–52] revealed that use of an external stent significantly reduced the incidence of PF compared with the no-stent group (OR 0·43, 0·27 to 0·68; $P < 0·001$). There were no significant differences in overall postoperative morbidity, DGE or overall mortality.

Internal stent *versus* no stent

Analysis of three OCS[20,48,50] revealed no significant differences between the two groups for all included outcomes.

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

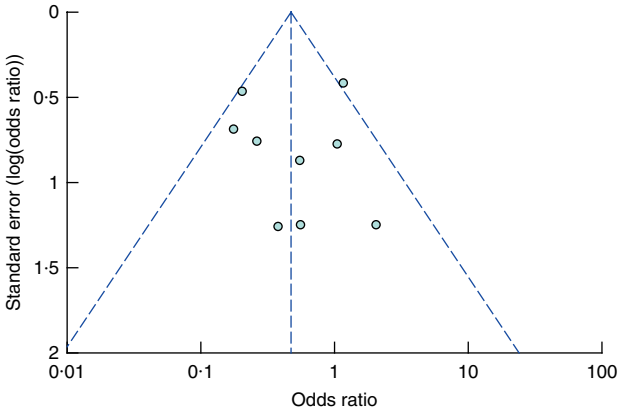


Fig. 4 Funnel plot of pancreatic fistula in included observational clinical studies. The plot revealed no publication bias

Publication bias

The funnel plot based on the incidence of PF (for OCS) is shown in *Fig. 4*. No study lay outside the limits of the 95 per cent c.i.

Discussion

Despite substantial improvement in perioperative outcomes of PD, a significant proportion of patients undergoing PD develop PF, which is still the most frequent cause of postoperative death[53,54]. A variety of strategies have been used to improve the safety of pancreatic–enteric anastomosis in recent years, based on technical or pharmacological approaches[10–14]. There are numerous theoretical reasons why a pancreatic stent should be useful in reducing PF formation, regardless of the type of stent used[55]. A stent may not only help to divert potentially destructive pancreatic juice away from the anastomosis site but may also allow more precise placement of sutures for the duct-to-mucosa anastomosis. It could also reduce the risk of iatrogenic pancreatic duct occlusion.

The placement of a pancreatic duct stent through the pancreatic anastomosis during PD has been reported with PF rates as low as 0–5 per cent in some instances, albeit in retrospective observational studies[28,56]. Few comparative studies have demonstrated the same effect[13,14,17,46]. Stents are not without drawbacks. Internal stents are assumed to fall spontaneously into the bowel lumen at a variable time after surgery[57]. On the other hand, external stents may lead to injury during stent removal as well as occasional pancreatitis and dilatation of the remnant pancreatic duct[44–46].

Although the present meta-analysis suggests that stents might reduce the incidence of PF, this is more evident from OCS than RCTs. This implies that current evidence is not sufficiently reliable to make a conclusion about their use. The effect seems more convincing for external stents. External stent use was associated with a reduced incidence of postoperative morbidity in RCTs, but consistent results were not obtained with analyses from OCS. Clearly, the number of total RCTs available was too small to allow a definitive interpretation. The external *versus* internal stent comparison also suffered from the lack of studies on the subject. The interstudy heterogeneity probably reflects different perioperative management strategies, definitions of outcome, and style and technique of PD in the various RCTs. In addition, results from the evaluation of OCS suggest that the incidence of postoperative morbidity, overall mortality, intra-abdominal fluid collections and DGE was not significantly different between the stent and no-stent groups.

Even though there was no heterogeneity in the non-randomized OCS included in the meta-analyses, there were still some limitations. The 11 included studies comprised a mixture of prospective and retrospective comparisons[9,17,19,20,46–52]. Second, other factors, such as use of adjunctive measures to decrease PF formation, texture of the pancreatic parenchyma (hard or soft), pancreatic duct diameter (more than 3 mm or smaller), the skill of the operating surgeon and even the definition of PF, may all have influenced outcome. In both RCTs and OCS, the interstudy heterogeneity and different clinical factors may have influenced the external validity of the summarized results. A meta-regression analysis to investigate further the heterogeneity in the studies could not be undertaken owing to the small number of included studies.

A number of factors might explain why a positive effect was not seen when both external and internal stents were analysed together, but the advantage stood out when external stents alone were investigated. An external stent diverts pancreatic juice away from the pancreaticojejunal anastomosis, preventing activation of pancreatic enzymes by bile that may lead to anastomotic breakdown[18,48]. Internal stents may provide limited protection of the pancreaticojejunal anastomosis against these activated enzymes[18]. External stents provide improved local control of secretions if an anastomotic leak occurs and may decompress the denervated jejunal segment better than internal stents[18,49].

The results of this meta-analysis should be interpreted with caution for a number of reasons. A significant proportion of data in the present study came from OCS. The number of RCTs included was probably too small to allow firm conclusions. There was evidence of interstudy heterogeneity with a potential to bias the results, probably

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

due to different patient characteristics, methods of adjuvant therapy, anastomotic technique and variability in assessing the outcome measures. The overall efficacy of pancreatic duct stent after PD remains a matter of discussion. The authors recommend further appropriately powered multicentre randomized controlled studies on the subject to guide future management.

Acknowledgements

J.J.X. and K.A. contributed equally to this work. The authors thank Professor Robert Sutton (Liverpool National Institute for Health Research Pancreas Biomedical Research Unit, Royal Liverpool University Hospital, University of Liverpool) for his continuous support as a Visiting Professor at Sichuan University.
Disclosure: The authors declare no conflict of interest.

References

1 Burcharth F, Olsen SD, Trillingsgaard J, Federspiel B, Moesgaard F, Struckmann JR. Pancreaticoduodenectomy for periampullary cancer in patients more than 70 years of age. *Hepatogastroenterology* 2001; **48**: 1149–1152.
2 Büchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. *Arch Surg* 2003; **138**: 1310–1314.
3 Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK *et al*. Pancreaticoduodenectomy with *en bloc* portal vein resection for pancreatic carcinoma with suspected portal vein involvement. *World J Surg* 2004; **28**: 602–608.
4 Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR *et al*. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000; **232**: 786–795.
5 Okamoto A, Tsuruta K. Fistulation method: simple and safe pancreaticojejunostomy after pancreatoduodenectomy. *Surgery* 2000; **127**: 433–438.
6 Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al*. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248–257.
7 Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. *Dig Surg* 2001; **18**: 453–457.
8 Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*.; International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005; **138**: 8–13.
9 Satoi S, Toyokawa H, Yanagimoto H, Yamamoto T, Hirooka S, Yui R *et al*. Is a nonstented duct-to-mucosa anastomosis using the modified Kakita method a safe procedure? *Pancreas* 2010; **39**: 165–170.
10 Kollmar O, Moussavian MR, Richter S, de Roi P, Maurer CA, Schilling MK. Prophylactic octreotide and delayed gastric emptying after pancreaticoduodenectomy: results of a prospective randomized double-blinded placebo-controlled trial. *Eur J Surg Oncol* 2008; **34**: 868–875.
11 Graham JA, Johnson LB, Haddad N, Al-Kawas F, Carroll J, Jha R *et al*. A prospective study of prophylactic long-acting octreotide in high-risk patients undergoing pancreaticoduodenectomy. *Am J Surg* 2011; **201**: 481–485.
12 Lillemoe KD, Cameron JL, Kim MP, Campbell KA, Sauter PK, Coleman JA *et al*. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2004; **8**: 766–772.
13 Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C *et al*. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. *Ann Surg* 2007; **246**: 425–433.
14 Pessaux P, Sauvanet A, Mariette C, Paye F, Muscari F, Cunha AS *et al*. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg* 2011; **253**: 879–885.
15 Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N *et al*. Reconstruction by pancreaticojejunostomy *versus* pancreaticogastrostomy following pancreatectomy: results of a comparative study. *Ann Surg* 2005; **242**: 767–771.
16 Ramacciato G, Mercantini P, Petrucciani N, Nigri GR, Kazemi A, Muroni M *et al*. Risk factors of pancreatic fistula after pancreaticoduodenectomy: a collective review. *Am Surg* 2011; **77**: 257–269.
17 Roder JD, Stein HJ, Böttcher KA, Busch R, Heidecke CD, Siewert JR. Stented *versus* nonstented pancreaticojejunostomy after pancreatoduodenectomy: a prospective study. *Ann Surg* 1999; **229**: 41–48.
18 Winter JM, Cameron JL, Campbell KA, Chang DC, Riall TS, Schulick RD *et al*. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. *J Gastrointest Surg* 2006; **10**: 1280–1290.
19 Imaizumi T, Hatori T, Tobita K, Fukuda A, Takasaki K, Makuuchi H. Pancreaticojejunostomy using duct-to-mucosa anastomosis without a stenting tube. *J Hepatobiliary Pancreat Surg* 2006; **13**: 194–201.
20 Smyrniotis V, Arkadopoulos N, Kyriazi MA, Derpapas M, Theodosopoulos T, Gennatas C *et al*. Does internal stenting of the pancreaticojejunostomy improve outcomes after pancreatoduodenectomy? A prospective study. *Langenbecks Arch Surg* 2010; **395**: 195–200.
21 Suzuki S, Kaji S, Koike N, Harada N, Tanaka S, Hayashi T *et al*. Pancreaticojejunostomy of duct to mucosa anastomosis can be performed more safely without than with a stenting tube. *Am J Surg* 2009; **198**: 51–54.

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

22 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
23 McKay A, Mackenzie S, Sutherland FR, Bathe OF, Doig C, Dort J *et al*. Meta-analysis of pancreaticojejunostomy *versus* pancreaticogastrostomy reconstruction after pancreaticoduodenectomy. *Br J Surg* 2006; **93**: 929–936.
24 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
25 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
26 Demets DL. Methods for combining randomized clinical trials: strengths and limitations. *Stat Med* 1987; **6**: 341–350.
27 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; **323**: 101–105.
28 Matsumoto Y, Fujii H, Miura K, Inoue S, Sekikawa T, Aoyama H *et al*. Successful pancreatojejunal anastomosis for pancreatoduodenectomy. *Surg Gynecol Obstet* 1992; **175**: 555–562.
29 Takao S, Shimazu H, Maenohara S, Shinchi H, Aikou T. Modified pancreaticogastrostomy following pancreaticoduodenectomy. *Am J Surg* 1993; **165**: 317–321.
30 Hiraoka T, Kanemitsu K, Tsuji T, Saitoh N, Takamori H, Akamine T *et al*. A method for safe pancreaticojejunostomy. *Am J Surg* 1993; **165**: 270–272.
31 Hamanaka Y, Suzuki T. Total pancreatic duct drainage for leakproof pancreatojejunostomy. *Surgery* 1994; **115**: 22–26.
32 Yoshimi F, Ono H, Asato Y, Ohta T, Koizumi S, Amemiya R *et al*. Internal stenting of the hepaticojejunostomy and pancreaticojejunostomy in patients undergoing pancreatoduodenectomy to promote earlier discharge from hospital. *Surg Today* 1996; **26**: 665–667.
33 Howard JM. Pancreatojejunostomy: leakage is a preventable complication of the Whipple resection. *J Am Coll Surg* 1997; **184**: 454–457.
34 Okamoto A, Tsuruta K. Fistulation method: simple and safe pancreaticojejunostomy after pancreatoduodenectomy. *Surgery* 2000; **127**: 433–438.
35 Takano S, Ito Y, Oishi H, Kono S, Yokoyama T, Kubota N *et al*. A retrospective analysis of 88 patients with pancreaticogastrostomy after pancreaticoduodenectomy. *Hepatogastroenterology* 2000; **47**: 1454–1457.
36 Dai XW, Ma K, Wang FX, Yang FQ, Wang BS, Zhao HY *et al*. Prevention of pancreaticojejunal anastomotic leakage after pancreaticoduodenectomy with separate internal drainage of bile and pancreatic fluid. *Hepatobiliary Pancreat Dis Int* 2003; **2**: 131–134.
37 Payne RF, Pain JA. Duct-to-mucosa pancreaticogastrostomy is a safe anastomosis following pancreaticoduodenectomy. *Br J Surg* 2006; **93**: 73–77.
38 Satoi S, Toyokawa H, Yanagimoto H, Yamamoto T, Yamao J, Kim S *et al*. A new guideline to reduce postoperative morbidity after pancreaticoduodenectomy. *Pancreas* 2008; **37**: 128–133.
39 Prenzel KL, Hölscher AH, Grabolle I, Fetzner U, Kleinert R, Gutschow CA *et al*. Impact of duct-to-mucosa pancreaticojejunostomy with external drainage of the pancreatic duct after pancreaticoduodenectomy. *J Surg Res* 2011; **171**: 558–562.
40 Grace PA, Pitt HA, Tompkins RK, DenBesten L, Longmire WP Jr. Decreased morbidity and mortality after pancreatoduodenectomy. *Am J Surg* 1986; **151**: 141–149.
41 Suzuki S, Kaji S, Koike N, Harada N, Hayashi T, Suzuki M *et al*. Pancreaticoduodenectomies with a duct-to-mucosa pancreaticojejunostomy anastomosis with and without a stenting tube showed no differences in long-term follow-up. *J Hepatobiliary Pancreat Sci* 2011; **18**: 258–262.
42 Imaizumi T, Harada N, Hatori T, Fukuda A, Takasaki K. Stenting is unnecessary in duct-to-mucosa pancreaticojejunostomy even in the normal pancreas. *Pancreatology* 2002; **2**: 116–121.
43 Kuroki T, Tajima Y, Kitasato A, Adachi T, Kanematsu T. Stenting *versus* non-stenting in pancreaticojejunostomy: a prospective study limited to a normal pancreas without fibrosis sorted by using dynamic MRI. *Pancreas* 2011; **40**: 25–29.
44 Kamoda Y, Fujino Y, Matsumoto I, Shinzeki M, Sakai T, Kuroda Y. Usefulness of performing a pancreaticojejunostomy with an internal stent after a pancreatoduodenectomy. *Surg Today* 2008; **38**: 524–528.
45 Tani M, Kawai M, Hirono S, Ina S, Miyazawa M, Shimizu A *et al*. A prospective randomized controlled trial of internal *versus* external drainage with pancreaticojejunostomy for pancreaticoduodenectomy. *Am J Surg* 2010; **199**: 759–764.
46 Sriussadaporn S, Pak-Art R, Sriussadaporn S, Kritayakirana K, Prichayudh S. Pancreaticoduodenectomy with external drainage of the pancreatic remnant. *Asian J Surg* 2008; **31**: 167–173.
47 Hakamada K, Narumi S, Toyoki Y, Nara M, Ishido K, Miura T *et al*. An easier method for performing a pancreaticojejunostomy for the soft pancreas using a fast-absorbable suture. *World J Gastroenterol* 2008; **14**: 1091–1096.
48 Lai EC, Chung NT, Yang GP, Li MK. Internal pancreatic ductal stenting to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a comparative study. *Hepatogastroenterology* 2011; **58**: 163–167.
49 Ohwada S, Tanahashi Y, Ogawa T, Kawate S, Hamada K, Tago KI *et al*. *In situ vs ex situ* pancreatic duct stents of duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy with Billroth I-type reconstruction. *Arch Surg* 2002; **137**: 1289–1293.
50 Matsusue S, Takeda H, Nakamura Y, Nishimura S, Koizumi S. A prospective analysis of the factors influencing pancreaticojejunostomy performed using a single method, in 100 consecutive pancreaticoduodenectomies. *Surg Today* 1998; **28**: 719–726.

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd

51 Tani M, Onishi H, Kinoshita H, Kawai M, Ueno M, Hama T *et al*. The evaluation of duct-to-mucosal pancreaticojejunostomy in pancreaticoduodenectomy. *World J Surg* 2005; **29**: 76–79.
52 Choe YM, Lee KY, Oh CA, Lee JB, Choi SK, Hur YS *et al*. Risk factors affecting pancreatic fistulas after pancreaticoduodenectomy. *World J Gastroenterol* 2008; **14**: 6970–6974.
53 Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F *et al*. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. *Am J Surg* 2009; **197**: 702–709.
54 van Berge Henegouwen MI, De Wit LT, Van Gulik TM, Obertop H, Gouma DJ. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage *versus* resection of the pancreatic remnant. *J Am Coll Surg* 1997; **185**: 18–24.
55 Poon RT, Lo SH, Fong D, Fan ST, Wong J. Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. *Am J Surg* 2002; **183**: 42–52.
56 Oida T, Mimastu K, Kawasaki A, Kuboi Y, Kano H, Amano S. Toward zero pancreatic leakage after pancreaticoduodenectomy for soft pancreas in low-volume pancreatic surgery centers. *Hepatogastroenterology* 2009; **56**: 886–890.
57 Ammori BJ, White CM. Proximal migration of transanastomotic pancreatic stent following pancreaticoduodenectomy and pancreaticojejunostomy. *Int J Pancreatol* 1999; **25**: 211–215.

© 2012 British Journal of Surgery Society Ltd
Published by John Wiley & Sons Ltd