Original Article on Pancreatic Cancer

Comparison of postoperative complications between internal and external pancreatic duct stenting during pancreaticoduodenectomy: a meta-analysis

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Background: Two types of pancreatic duct stents are used to improve postoperative outcomes of pancreatic anastomosis. The aim of this meta-analysis was to evaluate and compare the postoperative outcomes of patients with internal or external stenting during pancreaticoduodenectomy (PD).

Methods: We searched PubMed, EMBASE, the Cochrane Library and Web of Science databases until the end of December, 2014. Studies comparing outcomes of external *vs*. internal stent placement in PD were eligible for inclusion. Included literature was extracted and assessed by two independent reviewers.

Results: Seven articles were identified for inclusion: three randomized controlled trials (RCTs) and four observational clinical studies (OCS). The meta-analyses revealed that use of external stents had advantage on reducing the incidences of pancreatic fistula (PF) in total [odds ratio (OR) =0.69; 95% confidence interval (CI), 0.48-0.99; P=0.04], PF in soft pancreas (OR =0.30; 95% CI, 0.16-0.56; P=0.0002) and delayed gastric emptying (DGE) (OR =0.58; 95% CI, 0.38-0.89; P=0.01) compared with internal stents. There were no significant differences in other postoperative outcomes between two stenting methods, including postoperative morbidity (OR =0.93; 95% CI, 0.39-2.23; P=0.88), overall mortality (OR =0.70; 95% CI, 0.22-2.25; P=0.55), and intra-abdominal collections (OR =0.67; 95% CI, 0.26-1.71; P=0.40).

Conclusions: Based upon this meta-analysis, the use of external pancreatic stents might have potential benefit in reducing the incidence of PF and DGE. Due to the limited number of original studies, more RCTs are needed to further support our result and clarify the issue.

Keywords: Pancreatic duct stent; pancreaticoduodenectomy (PD); meta-analysis

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Introduction

Pancreaticoduodenectomy (PD) is the standard procedure commonly performed for benign and malignant diseases of the pancreas or periampullary region (1). Along with technical advances, PD has become a surgical procedure with a less than 5% operative mortality rate in specialized institutions around the world (1-3). Nevertheless, the surgical morbidity is still an issue bothering most pancreatic surgeons, as high as 30-40% of patients suffering from various complications (4,5), such as postoperative pancreatic fistula (PF), intra-abdominal collection and delayed gastric emptying (DGE).

PF, one of the most common major complications after PD with a frequency of 2-20% (6), contributes to the postoperative mortality (7). Therefore, a number of surgical strategies preventing PF after pancreatic resections have been attempted, including invagination anastomosis, duct-to-mucosa anastomosis, and other reconstruction routes (8,9); but none of them proved sufficiently effective to prevent PF adequately after pancreatectomy. More recently, pancreatic stenting has been recommended during pancreaticojejunostomy (PJ) to reduce the risk of PF (10,11). A pancreatic duct stent could support tube drainage of the pancreatic stump, by inserting a stent into the duct to make the pancreatic juice flow off directly after operations.

Two distinct methods are available for pancreatic stent insertion: internal and external stenting. Although most of the study results support that pancreatic stenting during PD (either internal or external) is associated with a decreased risk of PF when comparing to not placing stents (12-14), comparison of the efficacy between internal and external stenting has not been widely reported, and the association of stenting techniques and the relationship between stenting and common postoperative complications remains unclear.

This meta-analysis assessed the effectiveness of external and internal stenting by comparing the postoperative morbidities between two groups. The enlightenment of the preferred stenting strategy during PD in preventing PF could provide more reliable evidence for clinical decision-making and for guiding further clinical trials.

Methods

Literature search

The PubMed (Medline), EMBASE, the Cochrane Library, Web of Science databases and the Cochrane Clinical

Trials Registry were searched systematically for all articles published until the end of December 2014. The following search terms were used with the appropriate combinations: stent, stents, stenting, anastomosis, pancreatic resection, internal, external, *in situ*, *ex situ*, PD, PJ, pancreaticogastrostomy, Whipple, PF, pancreatic anastomosis, etc. Using Medical Subject Headings terms combined with free text terms.

All published studies were searched without any language restriction and searches were performed by two independent researchers. The search was broadened by extensive cross-checking of the reference lists of all retrieved articles. All search strategies were determined after numerous preresearches.

Study selection

We included these studies into the meta-analysis if they met all of the following inclusion criteria: (I) patients treated with PD due to benign or malignant disease of the pancreas or periampullary region; (II) undergoing a pancreatic duct stent placement during PJ anastomosis following PD; (III) comparing the postoperative outcomes of external stenting and internal stenting; (IV) reporting on the incidence of PF. Abstracts, case reports, letters, comments, reviews without original data, studies lacking control groups or appropriate data for extraction were excluded.

Two authors independently screened titles and abstracts of each paper to exclude studies that clearly did not meet the inclusion criteria, after Endnote X5 software was used to remove the duplicates. Full texts of those eligible studies for further review were obtained and evaluated. Any disagreements between the two authors were resolved by discussion. If the discussion did not resolve the disagreements, a third person would make a final decision on the eligibility of the study.

Data extraction

Data extracted from each eligible study included: titles, years of publication, country and districts, years of study, study design, type of stents, definitions of PF, number of patients (age, sex, etc.), the surgery technique, postoperative data, etc. Two reviewers independently extracted the data and then cross-checked. Any disagreements were resolved by the same method as study selection. Primary outcome indicated PF; PF in soft pancreas (15). Secondary outcome indicated postoperative morbidity, overall mortality, DGE and intra-abdominal collections.

Quality assessment

Qualitative assessment of randomized clinical trials (RCTs) was based on the Jadad scoring system (16), which assesses the descriptions of randomization, blinding, and withdrawals in the trials. The observational clinical studies (OCS) were assessed and scored on the following basis as described by McKay and colleagues (17): including assessment of data collection (prospective *vs.* retrospective); assignment to internal stent group or external stent group by means other than the surgeonna preference; and an explicit definition of PF. A study was given a score of 1 for each item and score 1-4 in total. The study was considered of high quality if the score was equal to 3 or more.

Statistical analysis

This meta-analysis was performed in accordance with the recommendations of the PRISMA statements (18). Meta-analysis was performed using the Review Manager (version 5.3.0) software application (19). Odds ratio (OR) and mean difference (MD) were respectively used for the analysis of dichotomous and continuous variables. Both were reported with 95% confidence interval (CI). Heterogeneity between studies was measured using the Mantel-Haenszel Chi-square test and I^2 value, and $I^2 \leq 50\%$ was considered statistically significant and indicated the presence of heterogeneity. Either fixed effects model or random effects model was applied to calculate the pooled effect base on the heterogeneity. Heterogeneity was assessed before random effects model was used. A value of $P<0.05$ was considered significant. The P values are not adjusted for multiple comparisons in this meta-analysis.

Data analysis was performed by comparing external stents versus internal stents. In the analysis of the primary outcome, funnel plots were constructed to evaluate potential publication bias (20).

Subgroup analysis

According to the different study designs in RCTs and OCS, the evaluation on the primary outcome, PF was stratified.

Results

Eligible studies

Our initial search strategies yielded 150 potential articles. The results of the literature search are shown in *Figure 1*, in

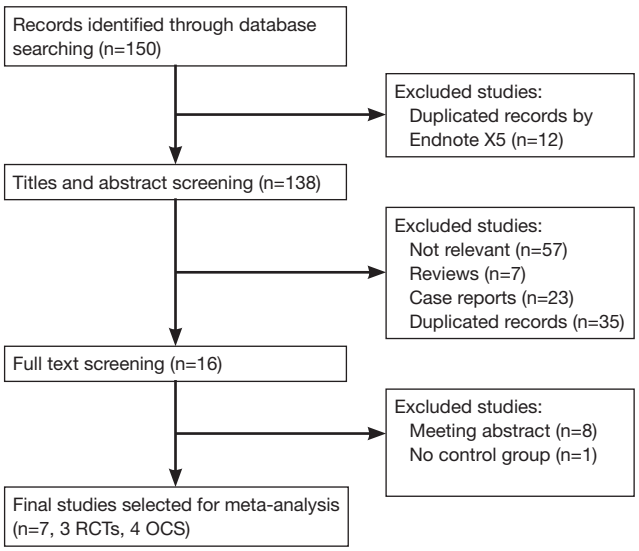

Figure 1 Study flow char.

which the PRISMA statement of the search flow is listed in detail.

Based on our selection criteria, seven studies was eventually included to this meta-analysis, including three randomized controlled studies (21-23) and four OCS (24-27). By using the Jadad scoring system, we accessed the quality of included RCTs and all the three RCTs were regarded as studies with good methodological quality. A total of 418 external stenting cases and 471 internal stenting cases enrolled from the seven eligible studies. Most of the populations selected in those studies come from Japan. The detailed characteristics of all the included studies are shown in *Table 1*.

Assessment of risk of bias of included RCTs

For the RCTs, we used the quality checklist recommended

Table 1 General characteristics of the studies included in the meta-analysis

Author	Year	Country	Design	Surgery	Group	Patients (n)	Gender (n, M/F)	Age (years)	Texture (soft/hard)	Anastomosis Technique	Definition of PF	Quality Score*
Wang (21)	2014	China	RCT	PD	EXS	110	59/51	52/58 (≥65/<65)	48/–	DM-PJ; IN-PJ	ISGF	3
					INS	109	54/55	56/53 (≥65/<65)	49/–			
Tani (22)	2010	Japan	RCT	PD	EXS	50	28/22	70 [44-87]	15/35	ES-DM-PJ	ISGPF	3
					INS	50	27/23	68 [25-84]	22/28			
Kamoda (23)	2008	Japan	RCT	PD/PPPD	EXS	22	8/14	9/13 (≥65/<65)	13/9	ES-DM-PJ; EE-IN-PJ	ISGPF, or JHH (23)	3
					INS	21	7/14	14/7 (≥65/<65)	12/9			
Meng (24)	2014	China	Retro	PD	EXS	128	76/52	44/84 (>65/≤65)	NS	EE-IN-PJ	ISGPF	2
					INS	188	110/78	53/135 (>65/≤65)	NS			
Ito (25)	2012	Japan	Retro	PD	EXS	43	–	–	34/9	ES-IN-PJ	ISGPF	2
					INS	37	–	–	20/17			
Ohwada (26)	2002	Japan	Retro	PD/PPPD	EXS	37	21/16	62±12	–	ES-DM-PJ	>3 times serum amylase in drainage fluid	1
					INS	37	23/14	63±10	–			
Yoo (27)	2014	Korea	Retro	PPPD	EXS	28	19/9	62.8±10.3	–	DM-PJ	ISGPF	2
					INS	29	19/10	65.2±7.9	–			

*, randomized clinical trials (RCTs) were scored according to the Jadad scoring system; the method of McKay and colleagues was used for non-randomized studies. PF, pancreatic fistula; RCT, randomized clinical trial; PD, pancreaticoduodenectomy; Retro, retrospective observational study; EXS, external stent; INS, internal stent; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreaticoduodenectomy; ES, end-to-side; EE, end-to-end; DM, duct-to-mucosa; IN, invagination; ISGPF, International Study Group on Pancreatic Fistula; JHH, Johns Hopkins Hospital.

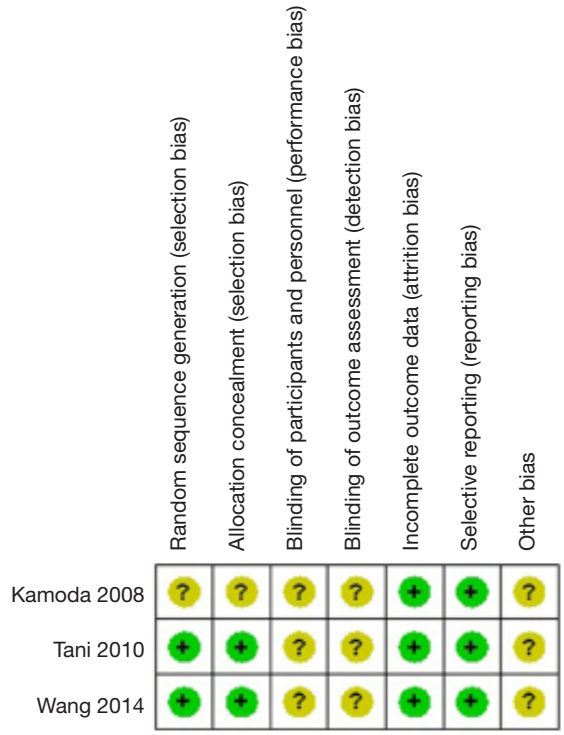

Figure 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included RCTs. RCT, randomized controlled trial.

in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (28). The quality checklist for assessing the risk of bias covered six headings (sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting bias, other potential sources of bias), where a response of "Yes" indicated a low risk of bias, "Unclear" indicated an uncertain risk of bias, and "No" indicated a high risk of bias. Any discrepancies were resolved by discussion among all review authors. The final results were showed in *Figure 2*.

Meta-analysis results

Primary outcome

Pancreatic fistula (PF)

All of the seven included trials reported the incidence of PF. However, Ito *et al.* reported the incidents of PF only in patients with soft pancreas rather than the patients in general (25). So we pooled data from the other six studies capable of comparing external stents with internal stents (21-27).

The meta-analysis results indicated that external stents had benefits on the reduction of PF occurrence with a lower rate of PF than internal stents (OR =0.69; 95% CI, 0.48-0.99; P=0.04; I^2=44% for heterogeneity). Due to a moderate heterogeneity in the pooled studies indicated by a 44% I^2, the data was further stratified according to the study design. It showed that there was no significant difference between the two stenting methods in the OCS subgroup (OR =1.10; 95% CI, 0.65-1.86; P=0.73; I^2=0% for heterogeneity), while the incidence of PF in external stents group was significantly lower than that in the internal stents group (OR =0.46; 95% CI, 0.28-0.75; P=0.002; I^2=0% for heterogeneity) in the subgroup analysis of RCTs (*Figure 3*).

The I^2 was 0% showing that there was no significant heterogeneity in the pooled RCTs or OCS subgroup.

Pancreatic fistula (PF) in soft pancreas

Three of seven trials (21,22,25) reported on PF in soft pancreas between external and internal stents. Pooled analysis (*Figure 4*) of these three studies showed that rate of PF in patients with soft pancreas was significantly lower in the external stents group than the internal stents group (OR =0.30; 95% CI, 0.16-0.56; P=0.0002; I^2=0% for heterogeneity). The I^2 was 0% showing that there was no significant heterogeneity in the pooled studies.

Secondary outcome measures

Delayed gastric emptying (DGE)

Six trials (21-26) reported on DGE between the external and internal stents group ($P_{heterogeneity}$=0.33, I^2=14%), and the fixed model was used. Pooled analysis (*Figure 5*) of the six studies indicated that there was a significant difference between the two groups (OR =0.58; 95% CI, 0.38-0.89; P=0.01).

Sensitivity analysis by using random effects model did not change the result.

Intra-abdominal fluid collections

Five trials (21-23,25,26) reported on intra-abdominal fluid collections ($P_{heterogeneity}$=0.75; I^2=0%) using a fixed model. There was no difference between the external and internal stents group (OR =0.67; 95% CI, 0.26-1.71; P=0.40). The I^2 was 0% indicating that there was no heterogeneity in the pooled studies (*Figure 6*).

Overall postoperative morbidity

Next, we examined the overall postoperative morbidities including PF, DGE and other postoperative complications such as gastrointestinal bleeding, pulmonary infection, and abdominal infection.

Three trials (21,22,26) compared the overall postoperative

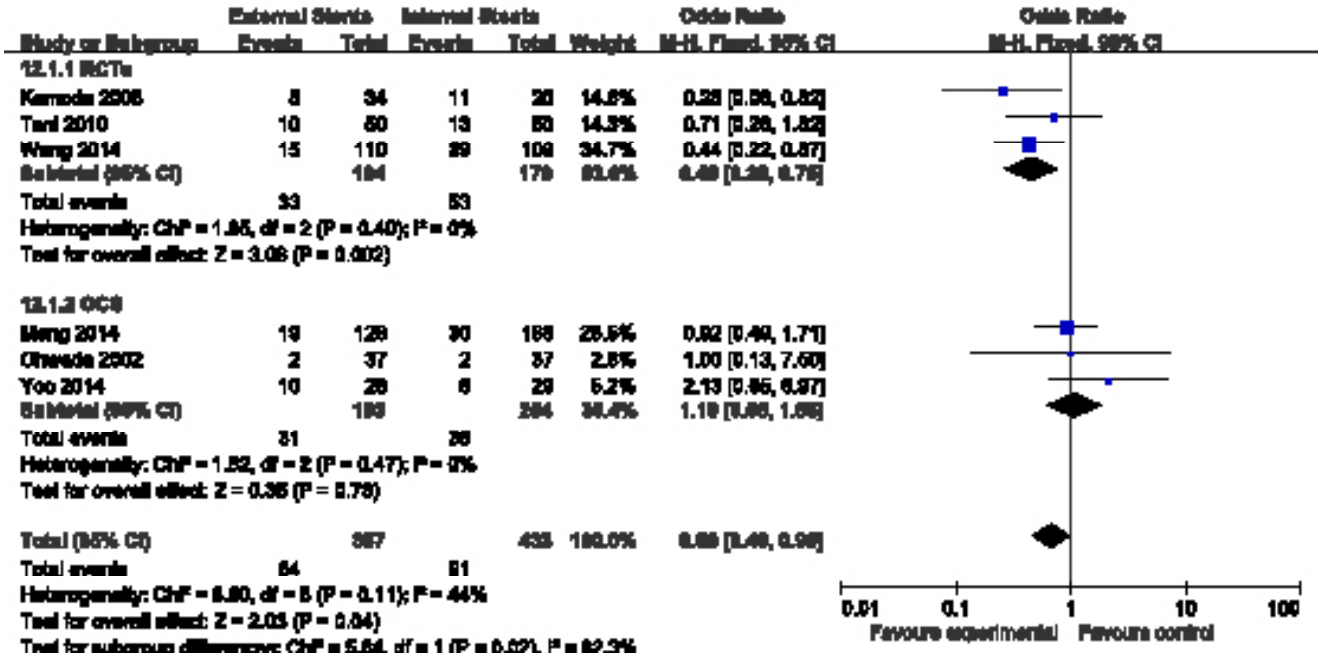

Figure 3 Meta-analysis of pancreatic fistula rate after pancreatic stenting (internal or external) for RCTs and OCS. RCT, randomized controlled trial; OCS, observational clinical study.

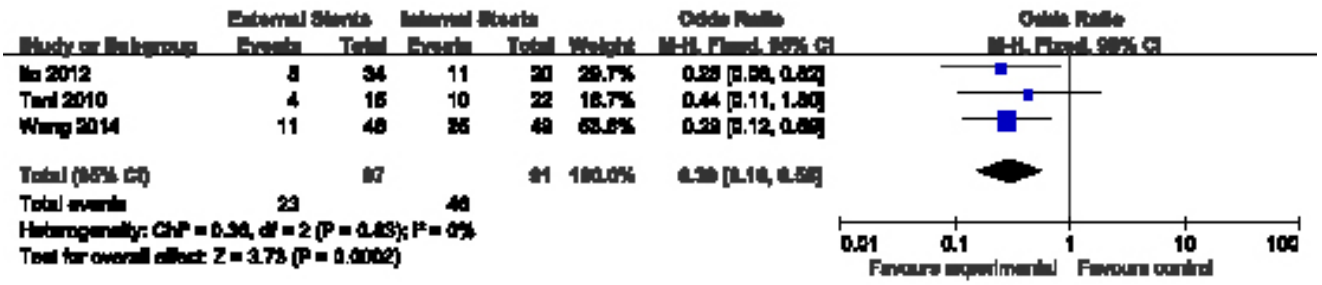

Figure 4 Meta-analysis of pancreatic fistula occurred after pancreatic stenting in soft pancreas by fixed effects model.

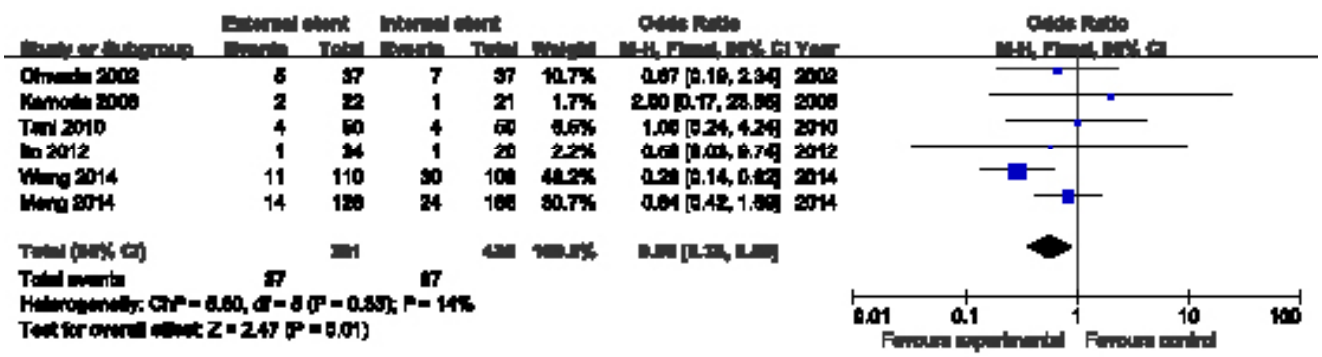

Figure 5 Meta-analysis for delayed gastric emptying in total with fixed effects model.

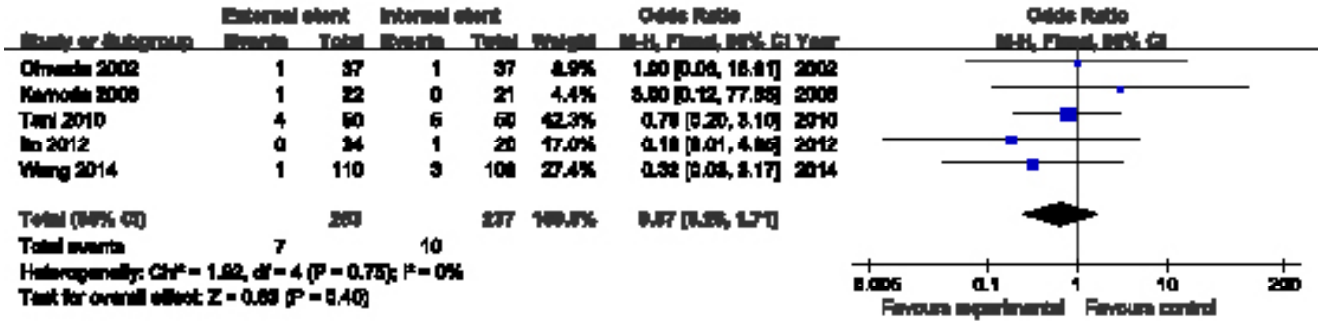

Figure 6 Meta-analysis for intra-abdominal collections in total with fixed effects model.

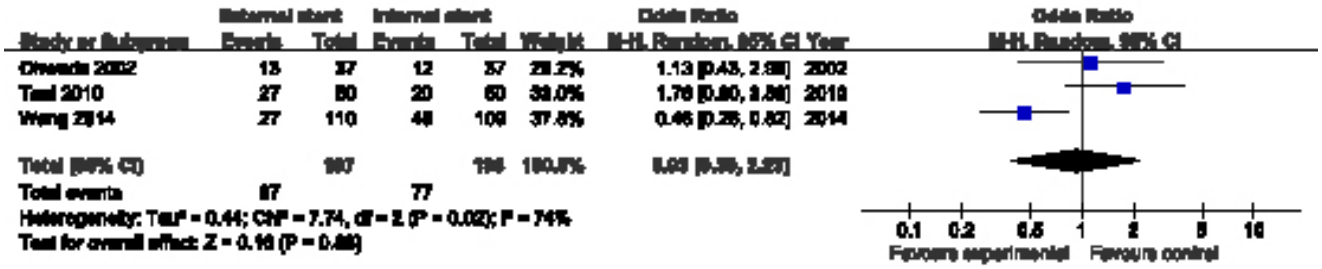

Figure 7 Meta-analysis for postoperative morbidity with random effect model.

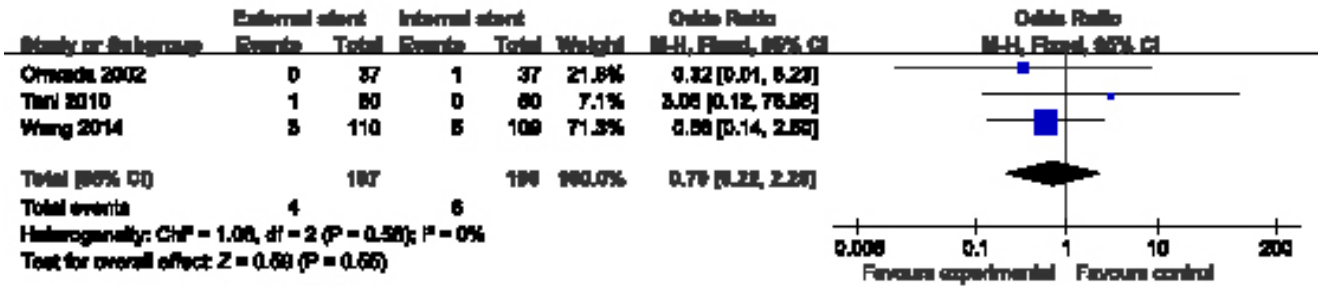

Figure 8 Meta-analysis for overall mortality in total with fixed effects model.

morbidity using a random model ($P_{heterogeneity}$=0.02, I^2=74%). Comparing with internal stents, the external stents had no benefit on the incidence of overall postoperative morbidity (OR =0.93; 95% CI, 0.39-2.23; P=0.88) (*Figure 7*). Although some degree of heterogeneity was present among these studies (I^2 =74%), use of the random-effects model did not change the result.

Overall mortality

Three trials (21,22,26) reported on overall mortality ($P_{heterogeneity}$=0.58, I^2=0%) and the fixed model was used. The pooled result (*Figure 8*) showed that there was no difference in the incidence of overall mortality between the external and internal stents groups (OR =0.70; 95% CI, 0.22-2.25; P=0.55). The I^2 was 0% indicating that there was no heterogeneity in the pooled studies.

Publication bias

The funnel plot based on the incidence of PF is shown in *Figure 9*. None of the studies evaluating external stents or internal stents lay outside the limits of the 95% CI, and most the studies were equally distributed around the vertical axis.

Discussion

This meta-analysis focused on the effect of stenting

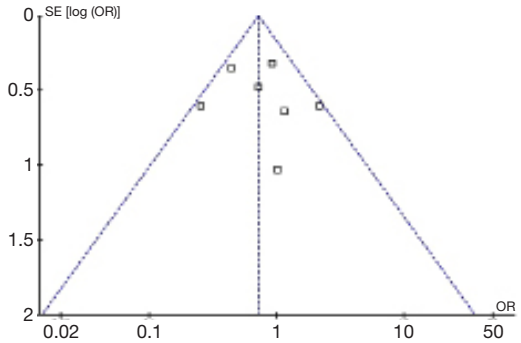

Figure 9 Funnel plot for the results from all included studies comparing pancreatic fistula in the external stents group and internal stents group.

techniques on the postoperative complications of PD. The present pooled results indicated that external stents had a higher benefit in reducing the rate of PF when comparing to internal stents. However, in the pooled analysis included both RCTs and OCS, a moderate heterogeneity of the results ($P_{heterogeneity}$=0.11; I^2=44%) give rise to a possibility that the reliability of the conclusion may be statistically influenced by study design, and heterogeneity among studies was decreased to zero when we meta-analyzed the RCTs and OCS respectively. PF occurred significantly less in the cases with external stents than internal stents used during PD (OR =0.46; 95% CI, 0.28-0.75; P=0.002; I^2=0%) in the subgroup of RCTs (*Figure 3*), and reduction in the incidence of PF after external stenting was found even more evident in patients with soft pancreas texture (OR =0.30; 95% CI, 0.16-0.56; P=0.0002; I^2=0%) (*Figure 4*).

Because of the occurrence of decreased gastrointestinal motility during the initial period after PD, pancreatic juice or bile more likely accumulates around the jejunal loop of the anastomosis. A stent may not only help to divert potentially destructive pancreatic juice away from the anastomosis site, but may also reduce the risk of iatrogenic pancreatic duct occlusion. Pancreatic stenting was useful in reducing PF formation, regardless of the type of stent used (29).

The use of an internal stent implies the placement of a plastic catheter across the PJ anastomosis for the drainage of pancreatic juice into the jejunum (30) whereas the external stent implies the placement of a plastic catheter into the main pancreatic duct for the external drainage of pancreatic juice (31). Some surgeons advocated that the use of an external pancreatic stent could reduce PF because the external pancreatic duct could drain pancreatic juice from the anastomosis more completely, preventing the activation of pancreatic enzymes and decrease the chance of stent migration compared with the use of an internal stent (32,33).

The texture of pancreas has been the most consistently linked to the risk of PF (10,21,25,33). A "soft pancreas" was defined as a pancreas with normal exocrine and endocrine functions, with a diameter of the main pancreatic duct less than 3 mm without apparent fibrosis, while a "hard pancreas", fibrotic pancreatic tissue with the diameter of the main pancreatic duct more than 3 mm, is considered to have compromised exocrine and endocrine functions (15). Given the key role of drainage in the management of postoperative complications, for patients with soft pancreatic tissue capable of secreting a considerable amount of pancreatic juice, an effective drainage of pancreatic juice after PD becomes extremely important. In this meta-analysis, a reduction in the incidence of PF was closely related to the type of pancreatic stents in the cases with soft pancreatic texture, which may indicate the superior drainage efficiency via external stents over internal stents particularly in the scenario of normal output of pancreatic juice.

The ISGPF grading system is commonly used for a universal definition of PF (6) in order to avoid unbalanced data yielded by different definitions compared in the studies of PF. In this meta-analysis, 6 out of the 7 included studies had reported the definition of PF based on ISGPF.

The meta-analysis also revealed that patients might benefit more from external stenting than internal stenting by reducing the incidence of DGE (OR =0.58; 95% CI, 0.38-0.89; P=0.01). Although the exact pathogenesis of DGE remains unclear, some studies found that PF is one of independent factors for DGE (34,35). Since DGE could be secondary to PF, the reduction in the rate of PF, to some extent, is expected to lead to the reduction in the incidence of DGE, which is in agreement with the significantly lower incidence of both PF and DGE in the external stenting group in this meta-analysis.

Difference between two stenting methods was not found in other postoperative outcomes, such as overall mortality, postoperative morbidity, intra-abdominal collections and pancreas atrophy. Pathogenesis of postoperative complications is usually complex and multifaceted. For instance, atrophy of the pancreatic parenchyma occurs frequently after PD, and often associated with physiological changes in the digestive function, poor pancreatic drainage through the site of the pancreaticojejunal anastomosis, and/or resection of the duodenum (36-38). In this mete-

analysis, only one study included pointed out the pancreatic atrophy rate after using external or internal pancreatic duct stents following PD; thus the pooled data was unable to be calculated. According to Yoo *et al.* (27), similar atrophy rates of the pancreatic parenchyma in both stenting groups following pylorus-preserving pancreaticoduodenectomy (PPPD), suggesting that an effective drainage may only play one contributing role and that the prevention and management of pancreas atrophy should be approached in a comprehensive manner.

The major limitation of this meta-analysis is the small number of clinical trials with high quality (RCTs) available for this meta-analysis. In addition, different patient characteristics, different anastomotic technique used by individual surgeons, and other factors causing variability among studies including definitions of PF, textures of pancreas, and methods for allocation concealment and blinding in RCTs, may all have contributed to the inter-study heterogeneity in assessing the outcome measures. Moreover, surgical experience and volumes in different centers that conducted the studies would have an impact on the outcomes of the studies selected by this meta-analysis. The efficacy of different pancreatic duct stenting strategies after PD remains to be further investigated through large multicenter randomized controlled studies.

Conclusions

From pool data to both RCTs and OCS, external stents were shown to reduce the incidence of PF especially in soft pancreas and have additional benefits by reducing the incidence of DGE comparing to internal stents. No difference was found in other postoperative outcomes with two different stenting approaches. Large multicenter RCTs are needed to provide more reliable evidence to help further establish the optimal stenting strategy in reducing postoperative complications, especially PF.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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