

Clinical efficacy of middle pancreatectomy contrasts distal pancreatectomy: a single-institution experience and review of literature

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Key words

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Introduction

Distal pancreatectomy (DP) is the standard surgical procedure for tumours in pancreatic body and tail for the past 20 years. However, it usually needs to remove the spleen simultaneously. Therefore, thrombosis and serious infections will place patients at a serious risk. In addition, the removal of excessive pancreatic tissue can also lead to pancreatic endocrine or exocrine insufficiency, which may affect the long-term quality of patients' life.¹

In 1957, Guillemin and Bessot first reported that middle pancreatectomy (MP) can be used to treat chronic pancreatitis and pancreatic transection injury.² For the benign and borderline tumours in the neck and body of the pancreas, the middle pancreatic resection can keep the normal pancreas tissue as much as possible, and the incidence of long-term post-operative pancreatic function

Abstract

Background: We aim to analyse the difference of clinical efficacy between middle pancreatectomy (MP) and distal pancreatectomy (DP).

Methods: A retrospective study was used to analyse 39 cases of MP and 52 cases of DP from the Department of Hepatopancreatobiliary Surgery of the Affiliated Hospital of Qingdao University from February 2007 to December 2016. Furthermore, we identify randomized controlled trials or strictly designed clinical controlled trials on MP and DP. We performed a meta-analysis of the final included studies using RevMan 5.3 software to illustrate the differences in efficacy between MP and DP.

Results: In the MP group, the operation time and diet start time were significantly longer than DP group. However, there was no significant difference in serious complications including clinically significant pancreatic fistula (grades B and C), delayed gastric emptying, reoperative and mortality. Furthermore, compared with DP, patients in MP group could benefit from long-term post-operative exocrine and endocrine function. Finally, we performed a meta-analysis including 14 studies with a total of 1104 patients and proved that the pancreatic fistula rate, endocrine and exocrine function were significantly different in the two groups.

Conclusion: The MP is a safe and feasible surgical method. It can well preserve the endocrine and exocrine function of pancreas and improve the life quality of patients.

insufficiency will be greatly reduced. However, MP might be accompanied by higher complication risks compared with DP due to the unavoidable reconstruction of digestive tract.³

However, the data of these studies regarding clinical efficacy vary significantly from different centre institution and the sample size of published studies on this topic was usually less than 30 cases. Moreover, there is lack of meta-analysis published regarding short- and long-term clinical outcomes on MP versus DP in the past 5 years.

In order to overcome the above limitations and thus generate a more precise estimate of the clinical efficacy difference between MP and DP, in this study, we illustrated our experience with patients who suffered from benign or low-grade malignant pancreatic lesions and accepted MP or DP at our institution during the past 10 years. Moreover, we systematically retrospect all relevant

published studies to evaluate the long-term operative outcomes and post-operative complications of MP and DP.

Methods

Patients

A total of 91 patients with benign or low-grade malignant pancreatic lesions underwent MP ($n = 39$) and DP ($n = 52$) from February 2007 to December 2016 in the Department of Hepatopancreatobiliary Surgery, Affiliated Hospital of Qingdao University. The patients employed in comparative analysis with the following criteria: (i) single benign or borderline tumour limited to the neck or proximal pancreas; (ii) the cases should be provided with iconography data including computed tomography (CT) scans, ultrasonography or endoscopic retrograde pancreatography; (iii) the clinical data of the patients are complete, including pathological findings, intra-operative indicators, post-operative complications items and long-term outcomes data; and (iv) patients who are amenable to either MP or DP. MP was applied when at least 5 cm of the distal remnant pancreas could be remained. The formal informed consent has been signed by all participants.

Outcome evaluations

For further comparative analysis, intra-operative indicators, post-operative variable complications and long-term outcomes during the follow-up were retrospectively gathered. We judge the patients suffered from pancreatic fistulas based on the rule of International Study Group of Pancreatic Fistula (ISGPF).⁴ Thereinto, the clinically significant pancreatic fistula rate was limited to grades B and C. To evaluate long-term functional outcomes, including endocrine and exocrine pancreatic function, patients were required to undergo clinical, radiological and laboratory evaluation every 6 or 12 months. The endocrine impairment was diagnosed as worsening diabetes that required more insulin control or new onset diabetes. This was diagnosed referring to the definitions stated by the World Health Organization.⁵ Steatorrhoea and weight loss (more than 3% pre-operative weight during follow-up), which improved with pancreatic enzyme supplement, were used as a criteria to determine whether endocrine deficiency happens or not.

Systematic review and meta-analysis

We searched the electronic databases PubMed, Embase and the Cochrane Library for literature search. We identified all studies that compared clinical effect that compared DP with MP until March 2018. Two authors of this study independently completed the literature search and data collection. The following search keywords were used: 'central/limited conservative middle/medial/median/segmental pancreatectomy versus distal/left pancreatectomy'.

Two assessors independently undertook the mission of extracting the following data from selected articles. The extracted content includes author, publication year, number of cases and the comparison items in MP with DP such as operative time, duration of hospitalization, morbidity, post-operative complications, pancreatic fistula, reoperation, long-term endocrine and exocrine function and loss ratios of follow-up.

The methodological quality of selected articles was evaluated using the Newcastle-Ottawa Scale.⁶ The quality was appraised

according to three items: patient selection, judgement of outcomes and comparability of MP and DP group. This standard change from zero to nine stars: integration of research with a score greater or equal to 6 was considered reasonable in method.

Researches with the following criteria were accepted: (i) literature published before March 2018; (ii) the inclusion cases should be diagnosed clearly and contain the post-operative comparison of DP and MP, including operative time, length of hospital stay and so on; and (iii) the type of literature is strictly controlled in randomized controlled trials (RCTs) or well-designed non-RCTs about post-operative comparison of DP and MP. At the same time, the following essays were excluded in our research: non-human studies, case report, expert opinions and reviews without original data.

Statistical analysis

The continuous variable results of comparative analysis are expressed as mean \pm standard deviation, and independent sample Student's and paired-samples t testing were used for comparison. Categorical variables, including reoperation, pancreatic fistula and endocrine and exocrine impairment, used the chi-squared test and Fisher's exact test according to cell counts. Differences in two groups were considered significant when the P -value is less than 0.05. SPSS 22.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for all data analyses.

In the meta-analysis, Review Manager (RevMan) version 5.3.0 software (The Cochrane Collaboration, Copenhagen, Denmark) was used to analyse extracted dates. The data of comparative studies of MP and DP were calculated referring to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Quality of Reporting of Meta-analyses (QUORUM).^{7,8} The dichotomous variables were estimated by risk ratio (RR), and the continuous variables were reckoned with weighted mean difference. A fixed-effect (Mantel-Haenszel) statistical model was applied in the study when the I^2 statistic was less than 50%. In contrary, random effects model was accepted. The funnel plot model was used to examine publication bias. It also suggested statistically significant if P -value is less than 0.05.

Results

Single-centre experience

Mean age was 50.18 ± 18.49 years for the MP group and 51.27 ± 12.79 years for the DP group and there were no statistical differences in MP and DP. The clinic pathological characteristics and iconography feature of the MP and DP are showed in Table S1 and Figure 1. Surgical outcomes are shown in Table S2. Two groups of surgeries were finished successfully; the mean operation time was significantly shorter in the DP group (220.96 ± 90.69 min versus 275.52 ± 88.78 min, $P = 0.006$). There were no operative deaths appeared in the two groups, nor were there reoperations over 30 days after operation. Diet start time after the surgical treatment in the MP group was 5.28 ± 2.22 days and 4.29 ± 1.05 days in DP group ($P < 0.05$). Post-operative duration of hospital stay was significantly longer in patients who underwent DP surgery (15.94 ± 4.88 days). Pancreatic fistula occurred in 44 subjects, which almost of these (43 cases) were type A leaks. There were no significant differences

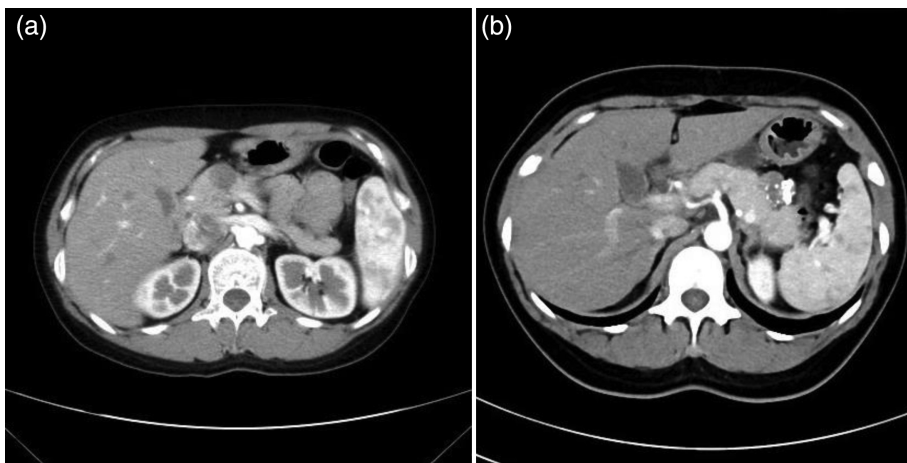


Fig. 1. Location of lesions in the pancreas. (a) Neck; (b) body.

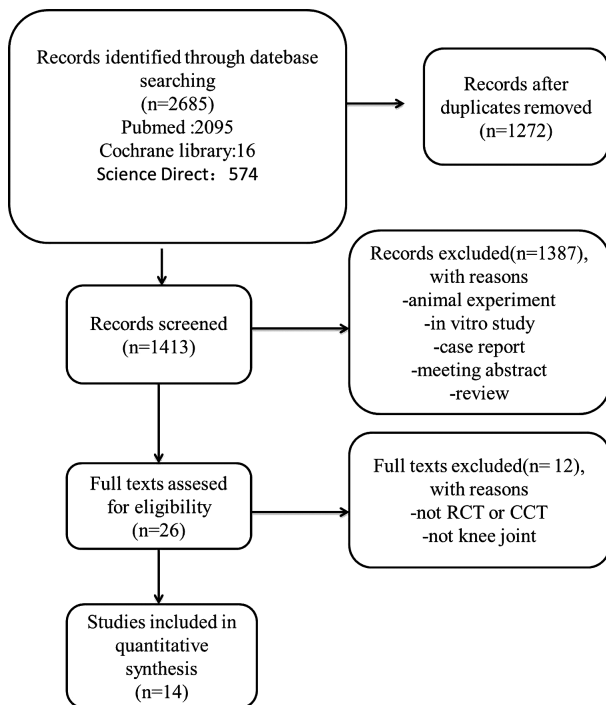


Fig. 2. Articles identified and evaluated during the review process.

in overall pancreatic fistula and clinical pancreatic fistula (grades B and C) between MP and DP. At the same time, we also did not observe significant difference in first flatus time and delayed gastric emptying based on clinical indexes review. Compared with the DP group patients, MP patients all had an excellent long-term exocrine function ($P < 0.05$). There were six patients appeared new onset diabetes mellitus and worsening diabetes during the follow-up in DP group compared with one patient in MP group ($P = 0.223$). Although no significant difference was obtained, there was a tendency in preserving endocrine function.

Literature meta-analysis

Literature review identified 2685 articles. Finally, 14 articles were included in our study.^{9–22} A total of 1104 patients were contained in this research, consisting of 432 patients undergoing MP and

672 patients undergoing DP. Figure 2 summarized the study flow. The risk of bias was evaluated according to the Newcastle-Ottawa Scale. Detailed information for each article is showed in Table S3.

The results of the meta-analysis were exhibited in Table S4. In the analysis of intra-operative indicators, two groups had statistically significant difference in operative time based on data extracted from 14 studies. MP takes longer than DP during the operation. (weighted mean difference 45.37 min; 95% confidence interval (CI) 17.39–75.35; $P < 0.05$). In addition, there was no observed weighted difference in other intra-operative items.

Post-operative pancreatic fistula was recorded in 12 studies. We proved that the pancreatic fistula rate was significantly higher in the MP group (RR 1.64; 95% CI 1.34–2.01; $P < 0.05$). The clinically significant pancreatic fistula rate (grades B and C, ISGPF) was provided from seven studies, However, we did not observe a statistically significant difference in two groups (RR 1.73; 95% CI 0.91–3.28; $P > 0.05$). These data and their publication bias were summarized in Figure 3.

The endocrine impairment was diagnosed as worsening diabetes that required more insulin control or new onset diabetes. The pooled data extracted from 12 studies indicated that MP preserved more function in pancreatic endocrine when compared with DP (RR 0.18; 95% CI 0.12–0.29; $P < 0.05$). Five studies provided compelling data for the exocrine insufficiency after the operation. In these studies, diarrhoea, faecal chymotrypsin levels, steatorrhea, weight loss (more than 3% pre-operative weight during follow-up) or needed pancreatic enzyme supplement can be used as criteria to determine whether endocrine deficiency happens or not. Compared with MP group, DP group had a significant disadvantage in exocrine insufficiency based on pooled results (RR 0.26; 95% CI 0.13–0.54; $P < 0.05$). These data and their publication bias were summarized in Figure 4.

Discussion

MP, also known as medial pancreatectomy, has been raised as a selective technique for better preserving pancreatic parenchyma and exocrine and endocrine functions. MP was first applied in 1957 and was performed in a patient who had trouble with chronic pancreatitis. Furthermore, MP has become the major choice for benign and

low malignant neoplastic and non-neoplastic lesions located in neck-body sections of the pancreas. For pancreatic tumour located in pancreatic body and tail, DP is the standard surgical procedure in the past 20 years.¹ However, the lately orientation in pancreatic surgery preferred conservative rather than radical resection for pancreatic carcinoma when oncological appropriate. Malignant pancreatic tumours are usually considered to spread lymphatic and venous drainage area around the tail of pancreas and the splenic hilum. Due to the incomplete dissection of soft tissue and nodes, MP cannot provide adequate tissue resection for cancers.¹⁷ Therefore, MP is just suitable for benign and low-malignant potential conditions in pancreatic carcinoma, and also in mucinous cystic neoplasms, solid pseudo papillary neoplasms, intra-ductal papillary mucinous neoplasms and other benign lesions.⁹

Our single-centre experience and meta-analysis both showed the MP group pay more time in operative progress. Previous study showed that this gap was probably caused by learning curve and the additional steps. Additional steps such as pancreaticogastrostomy or pancreaticojejunostomy in reconstruction of digestive tract could answer for the additional time.¹⁰ However, compared with function

preservation, it seems worth to pay more energy in operation. In the combined data for RCTs, although the truth that MP had a little difference in operative time (45.37 min), this did not lead to significant difference in blood loss and blood transfusion requirement between the two groups. Delayed gastric emptying has been accepted as mainly reason for post-operative morbidity after MP for inevitable gastrointestinal reconstruction in MP surgical process, which could destroy the balance of gastric and intestinal motility. However, we are not obtaining significant difference in our research and meta-analysis. This can be attributed to the increase of surgical skills and post-operative management levels. The patients who underwent MP have softer pancreatic parenchyma but same pancreatic duct with normal-calibre, which may be the main reason for the pancreatic fistula. Furthermore, the more intuitive reason is that the MP creates a more remnant pancreas than DP due to resection margin. Two regions could lead to the same risk of pancreatic leakage. Taking all factors into account, it may not be strange that pancreatic fistula rate in MP outstrip DP. In terms of long-term post-operative exocrine and endocrine function, MP group patients could benefit from function preservation significantly compared with DP in this study and meta-analysis. MP could preserve

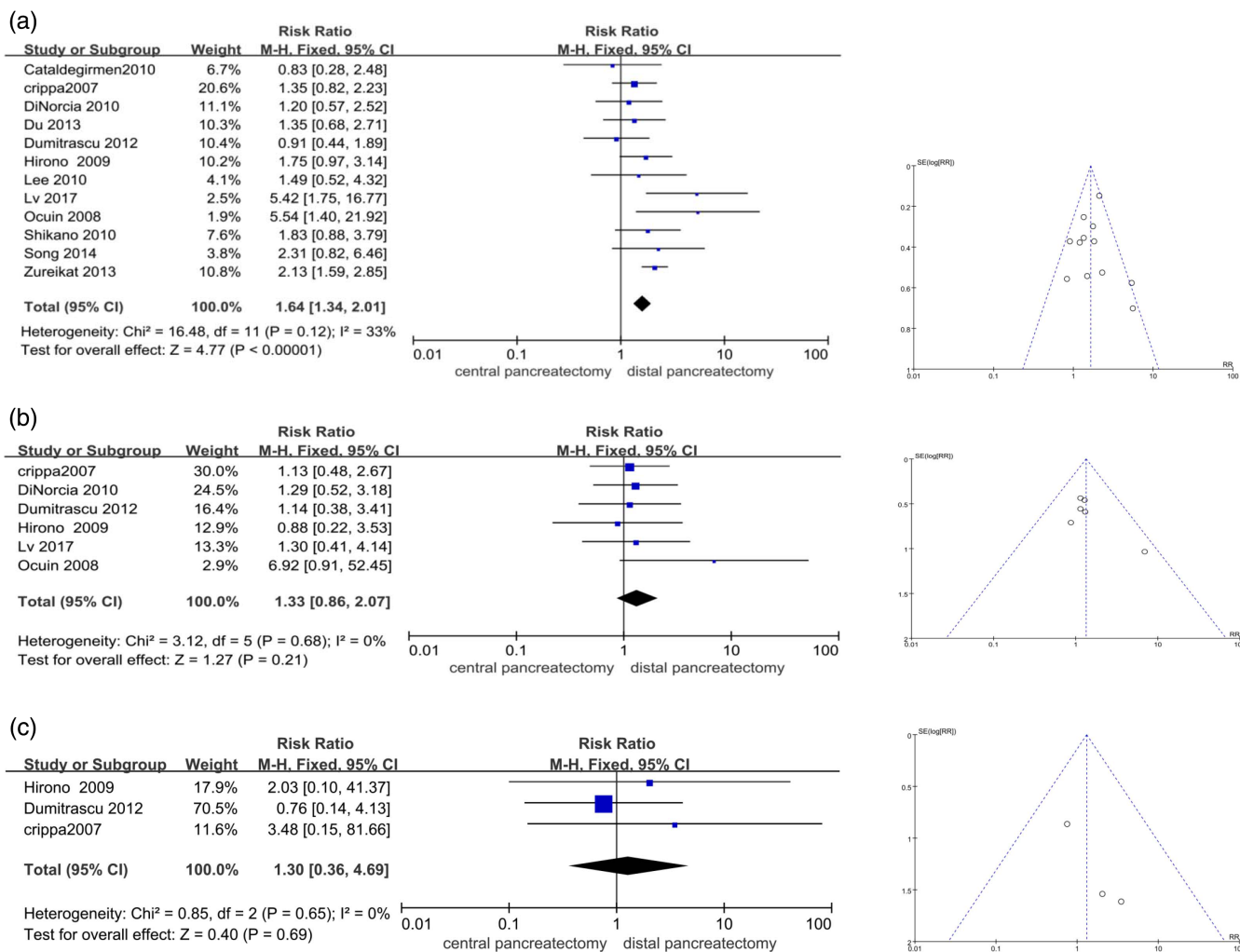


Fig. 3. The differences in post-operative outcomes and their publication bias. (a) The forest plot and Begg's funnel plot of overall pancreatic fistula. (b) The forest plot and Begg's funnel plot of pancreatic fistula (grades B and C). (c) The forest plot and Begg's funnel plot of delayed gastric emptying.

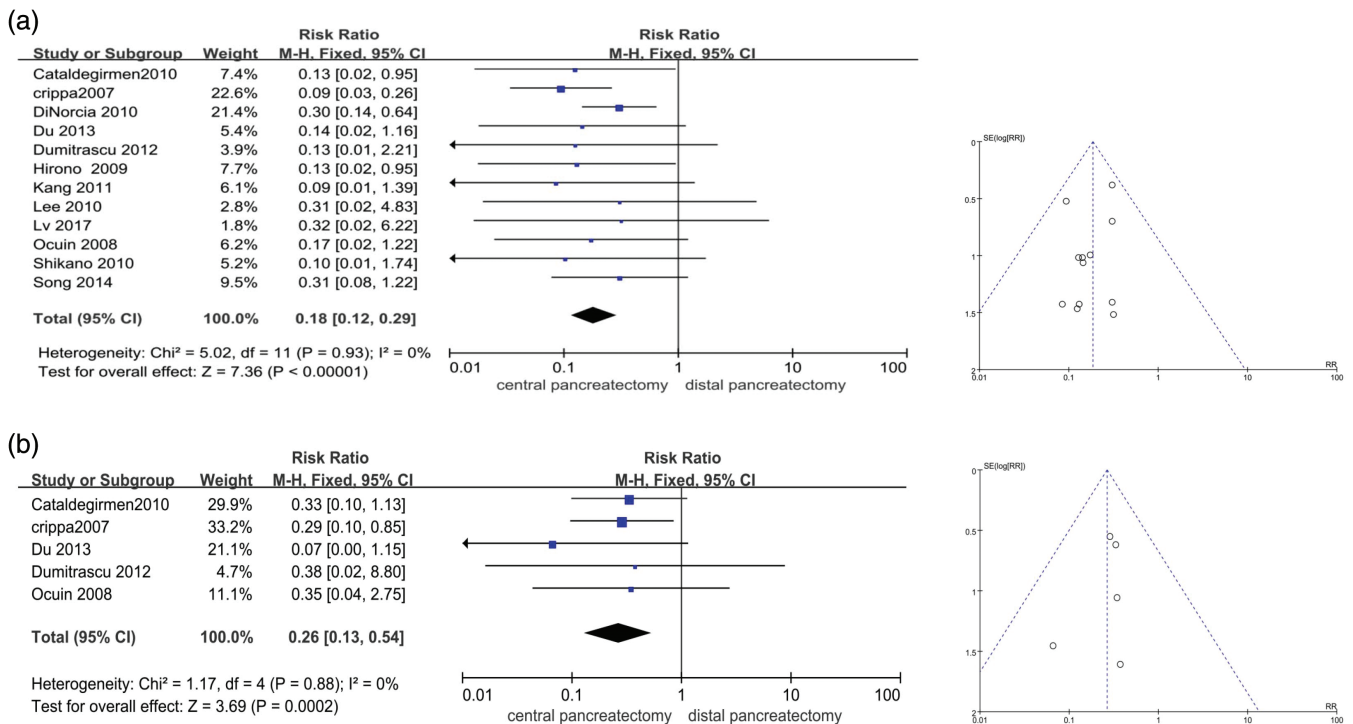


Fig. 4. The differences in long-term outcomes and their publication bias. (a) The forest plot and Begg's funnel plot of endocrine impairment. (b) The forest plot and Begg's funnel plot of exocrine insufficiency.

pancreatic parenchyma as much as possible during operation, particularly in body and tail of the parenchyma where there is an enrichment of islet cells. This result positively affirmed the previous researches.³ A growing body of literatures support that β -cells own the capacity of regeneration in childhood rather than adulthood. The adult pancreas loses the ability of islet exogenesis. The difference between MP and DP group in probability of new-onset or worsening diabetes mellitus was significant. In addition to losing more pancreas parenchyma, post-operative diabetes could be an important factor in exocrine insufficiency. The decreased level of insulin trophic and enzyme synthesis lead to the confusion of neural signals in pneumogastric nerve regulation and humoral regulation effect.

There are some limitations in our research. First of all, due to the inherent bias of retrospective cohort study, the baseline level was not accurately comparable. It is difficult to eliminate the influence of confounding factors in study selection. Besides, due to the limited surgical experience and post-operative management quality of the different surgeons, the heterogeneity of the included data is great. The extreme values such as operation time, blood loss and post-operative complications were obtained. There is still a need for high-quality, controlled trials to compare the differences in endocrine and exocrine functions of the pancreas between MP and DP. Regarding the lack of enough parameters, we could not generate more deep and significantly comparative results.

Conclusion

In summary, in terms of safety, our findings indicate that incidence of overall complications and pancreatic fistula in MP was much

higher. But in the severe complications, such as clinically significant pancreatic fistula (grades B and C), delayed gastric emptying, reoperation and mortality, the difference between MP and DP was not significant. In terms of efficacy, MP group patients benefit more from preserving endocrine and exocrine pancreatic functions in the long-term outcome compared with DP. We performed a fresh meta-analysis of available studies, containing the current study, to elucidate the efficacy and safety of MP versus DP. The combined data from RCTs also indicate the superiority and safety of MP. In accordance with the present results, these findings provide a rationale for MP as an acceptable and reliable procedure, especially in improving the quality of life of patients. However, a great deal of high-quality, controlled trials are required to test and verify this inference.

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Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Tumour factors of patients.

Table S2. Single centre outcomes.

Table S3. Characteristics of the studies included in the meta-analysis.

Table S4. Results of the meta-analysis.