



Effectiveness and safety of central pancreatectomy in benign or low-grade malignant pancreatic body lesions: a systematic review and meta-analysis

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Background: The best approach for treating benign or low-grade malignant lesions localized in the pancreatic neck or body remains debatable. Conventional pancreatoduodenectomy and distal pancreatectomy (DP) are associated with a risk of impairment of pancreatic function at long-term follow-up. With advances in technology and surgical skills, the use of central pancreatectomy (CP) has gradually increased.

Objectives: The objective was to compare the safety, feasibility, and short-term and long-term clinical benefits of CP and DP in matched cases.

Methods: The PubMed, MEDLINE, Web of Science, Cochrane, and EMBASE databases were systematically searched to identify studies published from database inception to February 2022 that compared CP and DP. This meta-analysis was performed using R software.

Results: Twenty-six studies matched the selection criteria, including 774 CP and 1713 DP cases. CP was significantly associated with longer operative time ($P < 0.0001$), less blood loss ($P < 0.01$), overall and clinically relevant pancreatic fistula ($P < 0.0001$), postoperative hemorrhage ($P < 0.0001$), reoperation ($P = 0.0196$), delayed gastric emptying ($P = 0.0096$), increased hospital stay ($P = 0.0002$), intra-abdominal abscess or effusion ($P = 0.0161$), higher morbidity ($P < 0.0001$) and severe morbidity ($P < 0.0001$) but with a significantly lower incidence of overall endocrine and exocrine insufficiency ($P < 0.01$), and new-onset and worsening diabetes mellitus ($P < 0.0001$) than DP.

Conclusions: CP should be considered as an alternative to DP in selected cases such as without pancreatic disease, length of the residual distal pancreas is more than 5 cm, branch-duct intraductal papillary mucinous neoplasms, and a low risk of postoperative pancreatic fistula after adequate evaluation.

Keywords: central pancreatectomy, distal pancreatectomy, pancreatic fistula

Introduction

With the widespread use of high-resolution abdominal imaging, the incidental diagnosis of benign or low-grade malignant pancreatic lesions has increased^[1,2]. Pancreatic resection is an essential treatment for benign or low-grade malignant lesions

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HIGHLIGHTS

- Most short-term complications after central pancreatectomy, including pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhage, length of hospital stay, the rates of overall and severe morbidity, and reoperation rate were statistically higher than those in patients undergoing distal pancreatectomy.
- A contour-enhanced funnel plot combined with a trim-and-fill method was used to determine whether the asymmetry in the funnel plot was due to publication bias. The results suggested that most of the missing studies were distributed within the white areas, indicating that the asymmetry in the funnel plot was due to publication bias.
- Central pancreatectomy should be considered as an alternative to distal pancreatectomy in selected cases such as without pancreatic disease, length of the residual distal pancreas is more than 5 cm, branch-duct intraductal papillary mucinous neoplasms, and a low risk of postoperative pancreatic fistula after adequate evaluation.

localized in the pancreatic neck or body and includes two main procedures: pancreatoduodenectomy (PD) and distal pancreatectomy (DP)^[3,4]. However, these surgical procedures result in a significant loss of normal pancreatic tissue, leading to a deficiency

in the patient's exocrine and endocrine functions. Tumor enucleation (EN) is appropriate for small and superficial lesions, which carry a risk of injury to the main pancreatic duct. Furthermore, EN is associated with a high risk for pancreatic leakage^[5].

In 1957, Guillemin and Bessot performed the first central pancreatectomy (CP) in a patient with chronic pancreatitis by anastomosing two pancreatic stumps with an omega-shaped jejunal loop^[6]. The indication of CP requires benign or low-grade malignant tumors without histological vascular invasion in the body of the pancreatic neck. In addition, the tumor has a distance between the right cut edge and the common bile duct, while the remaining pancreas is more than 5 cm after the left pancreas is severed^[7–9].

Compared to DP, CP avoids the loss of normal pancreatic tissue and, in theory, it is better at protecting the secretory function of the pancreas, reducing the incidence of long-term complications in patients. However, possibly due to an insufficient sample size, many studies have not concluded that there is a difference in long-term pancreatic secretory function between CP and DP^[10–13]. Therefore, a meta-analysis is required. Higher postoperative pancreatic fistulas (POPFs) and overall complications have been indicated in previous meta-analyses for mid-pancreatic resection than for DP^[14–18]. However, there were some shortcomings in the previous meta-analysis, including the omission of some published studies and the small sample size of the test group. Using our study as a benchmark, the aim of this paper is to compare the safety, feasibility, and short-term and long-term clinical benefits of CP and DP in matched cases.

Methods

This study was fully compliant with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines^[19], Supplemental Digital Content 1, <http://links.lww.com/JS9/A690> and was conducted and validated in accordance with AMSTAR2 guidelines^[20], Supplemental Digital Content 2, <http://links.lww.com/JS9/A691>. Our work has been reported in line with the PRISMA criteria^[19]. The study was registered through <http://www.researchregistry.com>, and the study number is reviewregistry1471.

Literature search strategy

Two investigators independently conducted an online literature retrieval or search of the PubMed, MEDLINE, Web of Science, Cochrane, and EMBASE databases from inception to February 2022, without restriction to regions, languages, or publication types. The search strategy was searched with the following search terms '(central pancreatectomy OR medial pancreatectomy OR middle pancreatectomy OR segmental pancreatectomy OR central pancreatic resection OR organ-preserving pancreatectomy OR parenchyma-preserving pancreatectomy OR organ-sparing pancreatectomy OR parenchyma-sparing pancreatectomy OR segmental pancreatic resection OR non-standard pancreatic resection OR non-standard pancreatic resection OR mesopancreatectomy OR mesopancreatectomy OR median pancreatectomy) AND (distal pancreatectomy OR left pancreatectomy)'. When multiple reports describing the same population over the same period were published, the most recent or highest-quality study was used. The references of the retrieved articles were

manually searched. We resolved any differences in opinion through a group discussion with a third author (D.W.) to reach a consensus.

Inclusion criteria

1. Study design: randomized controlled trials, case-matched controlled studies, retrospective cohort studies.
2. Study: studies comparing the clinical outcomes of CP and DP.
3. Participants: tumors with pathology of benign or low-grade malignant tumors in the pancreatic neck and proximal body.
4. Language: without restriction to languages.
5. Type of article: studies published as full-text articles.
6. Minimum sample size: ten patients among all age groups.

Exclusion criteria

1. Abstracts, letters, noncomparable or nonhuman studies, editorials, expert opinions, reviews without original data, and case reports.
2. Studies lacking the outcomes of interest.

Selection of studies

To ensure the standardization of the literature screening procedure, the evaluation staff will receive training, and the literature used will be prescreened. The selection process requires at least two independent evaluators (Shiyuan Bi and Jing Kong). Following the screening phase, papers that are deemed relevant by at least one of the reviewers will be subjected to a full-text review. To choose the suitable articles, two reviewers will independently screen the titles and abstracts. Any disagreements between the two reviewers will be resolved by discussion with a third reviewer (Yingyu Liu). The study selection process will be detailed in the systematic evaluation plan and the full text. The following steps are included (Fig. 1): select the studies and exclude any duplications with EndNote; read the title and abstract of each study to exclude unrelated studies that clearly do not meet the inclusion criteria; and analyze and determine any duplicated publications.

Data extraction

The following data were extracted: name of authors, study design, number of patients treated using surgical approaches (laparotomy, laparoscopy, and robotically assisted laparoscopy), age, intraoperative outcomes (operative time, intraoperative blood loss, and transfusion requirement), short-term postoperative outcomes (postoperative hospital stay, PF, clinically relevant PF, postoperative hemorrhage (POH), reoperation, overall morbidity, overall mortality, delayed gastric emptying (DGE), and intra-abdominal infection), and long-term outcomes (endocrine, exocrine functions, and tumor recurrence).

Quality assessment and statistical analysis

The levels of evidence were attributed according to the Oxford Center for Evidence-Based Medicine. The modified Newcastle–Ottawa scale (NOS) was used to appraise the methodological quality of the included studies^[8,21,22], which consisted of three factors: patient selection, comparability of the study groups, and assessment of outcomes. A score of 0–9 (allocated as stars) was assigned to each study, and observational studies receiving

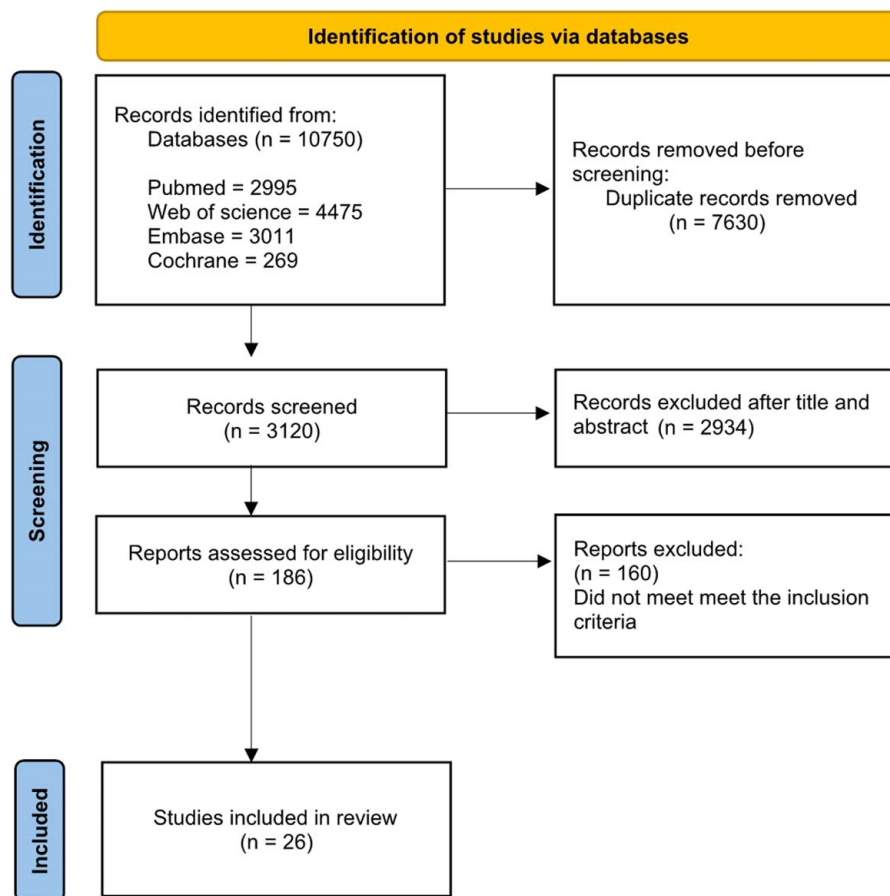


Figure 1. PRISMA flow diagram.

greater than or equal to seven stars considered to be of high quality.

Statistical analyses were performed using the R software (version 4.0.5). The mean difference (MD) and odds ratio (OR) were used to compare continuous and dichotomous variables, respectively. P value <0.05 were considered statistically significant. I^2 was used to represent statistical heterogeneity in these studies^[23]. Values less than 30% indicated low, 30–60% moderate, and $>60\%$ high heterogeneity. The Mantel–Haenszel fixed-effect method model or the Mantel–Haenszel random-effects heterogeneity method model was used according to the heterogeneity results. Publication bias was examined using a funnel plot and Egger's test. Publication bias was indicated by $P < 0.05$.

Validation of methodological quality

The methods applied in this systematic review and meta-analysis were implemented, critically appraised, and validated using AMSTAR 2^[20], Supplemental Digital Content 2, <http://links.lww.com/JS9/A691>, obtaining an overall rating of 'high' (16 points) (the scoring table was included in the supplementary materials), Supplemental Digital Content 3, <http://links.lww.com/JS9/A692>.

Results

The literature search resulted in a total of 10 750 studies before February 2022. No additional eligible studies were identified from other sources. Due to duplicity, 7630 articles were removed, and a further 2934 were eliminated following title and abstract screening based on the inclusion and exclusion criteria. Finally, 26 studies^[8,10–13,21,22,24–42], representing 774 CP and 1713 DP cases, were included in this meta-analysis. Figure 1 PRISMA flow diagram illustrates the identification and selection of studies, Supplemental Digital Content 4, <http://links.lww.com/JS9/A693>, and Table 1 describes the characteristics of the included articles. Among these 26 studies, eight were conducted in China^[11–13,25–27,31,32], four in Korea^[28–30,37], three in the USA^[22,35,36], two in Italy^[24,33], two in Germany^[21,34], three in Japan^[39–41], and one each in Romania^[10], Spain^[38], France^[42], and one combined study in the USA and Italy^[8]. The results of the meta-analysis and details of the surgery are summarized in Table 2 and Table 3, respectively.

Intraoperative outcomes

Operative time

A total of 23 studies, with 697 patients in the CP group and 1532 patients in the DP group, reported the operative time. There was a significantly shorter operative time in the DP group when

Table 1
Characteristics of included studies.

References	Country	Group (CP/DP)	Sex (M/F)	Study type	Quality scores	ISGPF
Yamafuchi <i>et al.</i> ^[41]	Japan	10/47	27/30	Retrospective	7	No
Falconi <i>et al.</i> ^[24]	Italy	21/64	—	Retrospective	7	No
Balzano <i>et al.</i> ^[33]	Italy	32/21	16/37	Retrospective	8	No
Müller <i>et al.</i> ^[21]	Germany	40/40	38/42	Prospective	8	Yes
Crippa <i>et al.</i> ^[8]	Italy-USA	100/45	37/108	Prospective	7	Yes
Ocuin <i>et al.</i> ^[22]	USA	13/18	8/23	Retrospective	9	Yes
Hirono <i>et al.</i> ^[40]	Japan	24/28	19/33	Prospective	7	Yes
Lee <i>et al.</i> ^[30]	Korea	14/188	73/129	Retrospective	8	Yes
Shikano <i>et al.</i> ^[39]	Japan	26/35	30/31	Retrospective	7	Yes
Cataldegirmen <i>et al.</i> ^[34]	Germany	35/35	34/36	Retrospective	7	Yes
DiNorcia <i>et al.</i> ^[36]	USA	50/50	26/74	Retrospective	7	Yes
Kang <i>et al.</i> ^[29]	Korea	17/22	15/24	Retrospective	7	Yes
Dumitrascu <i>et al.</i> ^[10]	Romania	22/25	11/36	Retrospective	7	Yes
Xiang <i>et al.</i> ^[26]	China	44/55	36/63	Retrospective	7	Yes
Zhan <i>et al.</i> ^[27]	China	10/16	—	Retrospective	7	Yes
Du <i>et al.</i> ^[25]	China	36/26	20/42	Retrospective	8	Yes
Zureikat <i>et al.</i> ^[35]	USA	13/83	—	Retrospective	7	Yes
Herrera-Cabezón <i>et al.</i> ^[38]	Spain	10/105	57/58	Prospective	7	Yes
Song <i>et al.</i> ^[28]	Korea	40/96	42/94	Retrospective	8	Yes
Dokmak <i>et al.</i> ^[42]	France	35/165	74/126	Prospective	7	No
Lv <i>et al.</i> ^[11]	China	16/26	11/31	Retrospective	7	Yes
Zhang <i>et al.</i> ^[12]	China	23/36	19/40	Retrospective	7	Yes
Chen <i>et al.</i> ^[32]	China	30/353	129/254	Retrospective	7	Yes
Lee <i>et al.</i> ^[37]	Korea	55/55	34/76	Retrospective	8	Yes
Shi <i>et al.</i> ^[13]	China	38/38	49/27	Retrospective	7	Yes
Cai <i>et al.</i> ^[31]	China	20/41	17/44	Retrospective	8	Yes

compared to the CP group [mean ($\pm$ SD): 208.61 ($\pm$ 80.86) vs. 248.22 ($\pm$ 76.74)] min (MD: 49.22; 95% CI: 32.07–66.37; $P < 0.0001$) (Fig. 2A).

Blood loss

Nineteen studies, with a total of 1767 patients reported data on blood loss. Compared to the CP group ($n = 564$), patients in the DP group ($n = 1203$) had greater estimated blood loss [mean ($\pm$ SD): 409.82 ($\pm$ 483.77) vs. 352.27 ($\pm$ 419.20) ml, and MD: – 63.74; 95% CI: – 116.49 to – 11.00; $P < 0.01$] (Fig. 2B).

Transfusions

Seventeen studies included this outcome. Intraoperative blood transfusions were observed in 7.4% (37/497) of patients in the CP group and 6.7% (80/1186) in the DP group. These were not statistically different (OR: 0.69, 95% CI: 0.44–1.07; $P = 0.0999$) (Fig. 2C).

Postoperative outcomes

Pancreatic fistula (PF)

All of the included studies reported the overall PF rate. It was higher in the CP group ($n = 286$, 36.9%) than in the DP group ($n = 346$, 20.2%) (OR: 2.25, 95% CI: 1.81–2.81; $P < 0.0001$) (Fig. 3A). Clinically relevant PF, considered Grades B or C according to International Study Group on Pancreatic Fistula Definition criteria^[43], was reported by 20 studies and was also significantly higher in the CP group ($n = 167$, 26.3%) than in the DP group ($n = 179$, 12.9%) (OR: 2.73; 95% CI: 2.09–3.58; $P < 0.0001$) (Fig. 3B).

Postpancreatectomy hemorrhage (POH)

POH was compared in 17 studies, and CP ($n = 43$, 7.9%) was associated with a significantly higher risk of POH than DP ($n = 32$, 3.2%) (OR: 2.80; 95% CI: 1.73–4.55; $P < 0.0001$) (Fig. 3C). In the DP group, major bleeding episodes did not occur in four studies, and not at all in the CP group.

Reoperation

Comparative data of reoperation were pooled from 19 studies. Significant differences were observed between the CP ($n = 33$, 6.3%) and DP groups ($n = 41$, 3.7%) (OR: 1.74; 95% CI: 1.09–2.76; $P = 0.0196$) (Fig. 3D).

Delayed gastric emptying (DGE)

Twelve studies reported DGE. The DP group ($n = 25$, 2.7%) had a reduced incidence of DGE compared to the CP group ($n = 20$, 5.3%) (OR: 2.56; 95% CI: 1.26–5.19; $P = 0.0096$) (Supplementary Fig. 1a, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Length of hospital stay (LOS)

We identified 21 studies with data on hospital stays. The LOS in the CP group was 5.03 days longer than that in the DP group (MD: 5.03; 95% CI: 2.42–7.63; $P = 0.0002$) (Supplementary Fig. 1b, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Severe morbidity

Eleven studies reported the rate of severe morbidity (Clavien–Dindo classification grade III or above). Significantly higher rates of severe postoperative complications were reported in the CP group ($n = 67$, 21.8%) than in the DP group ($n = 114$, 12.8%) (OR: 2.20; 95% CI: 1.50–3.22; $P < 0.0001$) (Supplementary Fig. 1c, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Mortality

Perioperative mortality was reported in 22 of the 26 studies. There were four deaths in total: three in the CP group (0.45%) and one in the DP (0.06%) group (OR: 3.60; 95% CI: 0.69–18.83; $P = 0.1286$) (Supplementary Fig. 1d, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Table 2
Patient outcomes in CP and DP.

	Studies	CP/DP	OR or MD	95% CI	P	I ² (%)	Model	Egger test's P
Intraoperative outcome								
Operative time (min)	23	697/1532	49.22	[32.07, 66.37]	< 0.0001	90.3	Random	0.074
Blood loss (ml)	19	564/1203	-63.74	[-116.49, -11.00]	< 0.0100	75.7	Random	0.419
Blood transfusion (n)	17	497/1186	0.69	[0.44, 1.07]	0.0999	0	Fixed	0.499
Early postoperative outcome								
PF	26	774/1713	2.25	[1.81, 2.81]	< 0.0001	28.6	Fixed	0.019
PF (grade B + C)	20	636/1391	2.73	[2.09, 3.58]	< 0.0001	41.8	Fixed	0.051
DGE	12	404/952	2.56	[1.26, 5.19]	0.0096	0	Fixed	0.099
POH	17	571/1041	2.80	[1.73, 4.55]	< 0.0001	7.2	Fixed	0.981
intraabdominal abscess/effusion	10	361/826	1.88	[1.12, 3.16]	0.0161	3.2	Fixed	0.924
LOS	21	635/1544	5.03	[2.42, 7.63]	0.0002	84.5	Random	0.020
Reoperation	19	588/1149	1.74	[1.09, 2.76]	0.0196	36.1	Fixed	0.209
Morbidity	21	650/1387	2.40	[1.91, 3.00]	< 0.0001	44.0	Fixed	0.010
Severe surgical complications	11	307/890	2.20	[1.50, 3.22]	< 0.0001	45.7	Fixed	0.367
Perioperative mortality	22	671/1533	3.60	[0.69, 18.83]	0.1286	0	Fixed	—
Long-term postoperative outcome								
Endocrine insufficiency	19	615/912	0.23	[0.16, 0.33]	< 0.0001	0	Fixed	0.490
DM worsening	10	369/571	0.19	[0.08, 0.47]	< 0.0001	0	Fixed	—
Exocrine impairment	13	421/410	0.49	[0.31, 0.79]	0.0030	0	Fixed	0.240
NODM	17	551/819	0.23	[0.15, 0.35]	< 0.0001	0	Fixed	0.139
Recurrence	10	320/470	1.52	[0.65, 3.52]	0.3336	0	Fixed	—

DGE, delayed gastric emptying; LOS, length of hospital stay; NODM, new-onset diabetes mellitus; PF, pancreatic fistula; POH, postoperative hemorrhage.

Table 3
Technical approaches and pathology of included studies.

References	Approach	CP		Benign or borderline (CP/DP)	Malignant (CP/DP)	Tumor diameter (cm) (CP/DP)
		PG	PJ			
Yamafuchi <i>et al.</i> ^[41]	Open	—	—	10/47	0/0	—
Falconi ^[24]	Open	—	—	—	—	—
Balzano <i>et al.</i> ^[33]	Open	0	10	32/21	0/0	—
Müller <i>et al.</i> ^[21]	Open	0	40	36/36	4/4	—
Crippa <i>et al.</i> ^[8]	Open	5	95	93/17	7/28	2.6 ± 1.9/4.9 ± 4.0
Ocuin <i>et al.</i> ^[22]	Open	7	6	13/18	0/0	3.2 ± 1.7/3.1 ± 2.0
Hirono <i>et al.</i> ^[40]	Open	3	21	20/24	4/4	3.0 ± 1.0/3.5 ± 2.0
Lee <i>et al.</i> ^[30]	Open	—	—	14/121	0/22	—
Shikano <i>et al.</i> ^[39]	Open	24	2	24/33	2/2	—
Cataldegirmen <i>et al.</i> ^[34]	Open	—	—	32/34	3/1	—
DiNorcia <i>et al.</i> ^[36]	Open, laparoscopic	71	2	50/46	0/4	2.0 ± 0.4/2.7 ± 0.9
Kang <i>et al.</i> ^[29]	Open, robotic	3	16	17/22	0/0	—
Dumitrascu <i>et al.</i> ^[10]	Open, laparoscopic, and robotic	0	22	19/21	3/4	4.5 ± 3.4/4.9 ± 3.6
Xiang <i>et al.</i> ^[26]	Open	13	31	44/55	0/0	—
Zhan <i>et al.</i> ^[27]	Robotic	—	—	—	—	—
Du <i>et al.</i> ^[25]	Open	14	22	36/26	0/0	2.6 ± 1.4/3.1 ± 1.3
Zureikat <i>et al.</i> ^[35]	Open, Robotic	—	—	—	—	—
Herrera-Cabezón <i>et al.</i> ^[38]	Open	—	—	10/67	0/20	—
Song <i>et al.</i> ^[28]	Open, laparoscopic	0	40	40/96	0/0	2.5 ± 1.2/4.0 ± 2.4
Dokmak <i>et al.</i> ^[42]	Open, laparoscopic	—	—	25/102	10/63	2.1 ± 0.9/3.5 ± 2.2
Lv <i>et al.</i> ^[11]	Open	9	7	16/26	0/0	4.6 ± 3.0/3.7 ± 2.3
Zhang <i>et al.</i> ^[12]	Laparoscopic	0	23	23/36	0/0	2.7 ± 0.7/3.2 ± 0.9
Chen <i>et al.</i> ^[32]	Laparoscopic, open	0	30	30/270	0/83	—
Lee <i>et al.</i> ^[37]	Open	45	10	55/55	0/0	—
Shi <i>et al.</i> ^[13]	Open	38	0	38/38	0/0	2.5 ± 1.4/2.6 ± 1.5
Cai <i>et al.</i> ^[31]	Laparoscopic	0	20	20/41	0/0	2.8 ± 0.8/3.6 ± 2.2

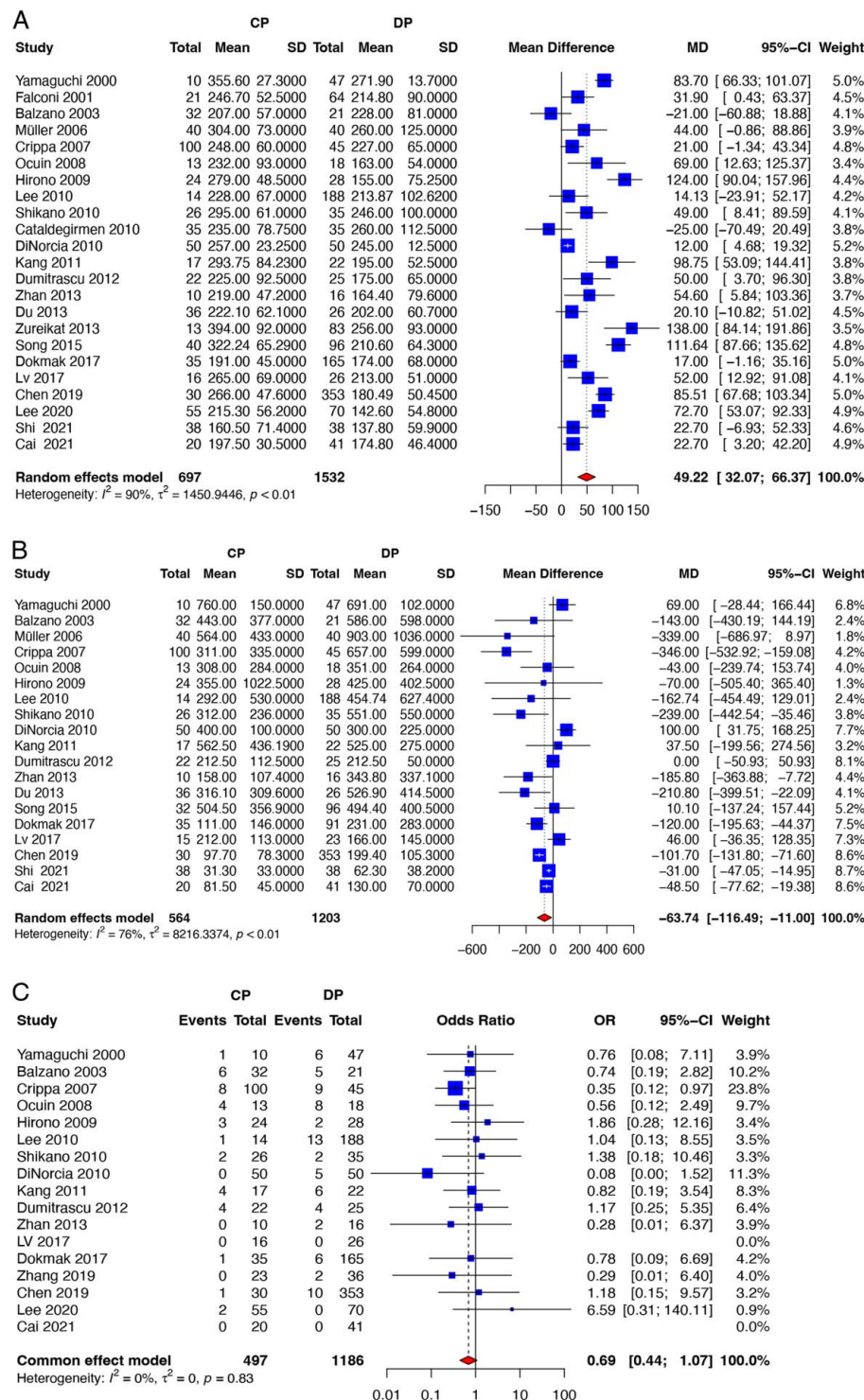


Figure 2. Forest plots of meta-analysis. A operative time; B blood loss; C transfusions.

Morbidity

The incidence of morbidity was reported in 21 studies. The results suggested that the CP group ($n = 326$, 50.2%) had higher rates of associated complications than the DP group ($n = 471$, 33.9%) (OR: 2.40; 95% CI: 1.91–3.00; $P < 0.0001$) (Supplementary Fig. 2a, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Intra-abdominal abscess or effusion

Intra-abdominal abscess or effusion data were recorded in 10 trials. Compared with the DP group ($n = 45$, 5.4%), the CP group ($n = 41$, 11.4%) had higher odds of intra-abdominal abscess or effusion (OR: 1.88; 95% CI: 1.12–3.16; $P = 0.0161$) (Supplementary Fig. 2b, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

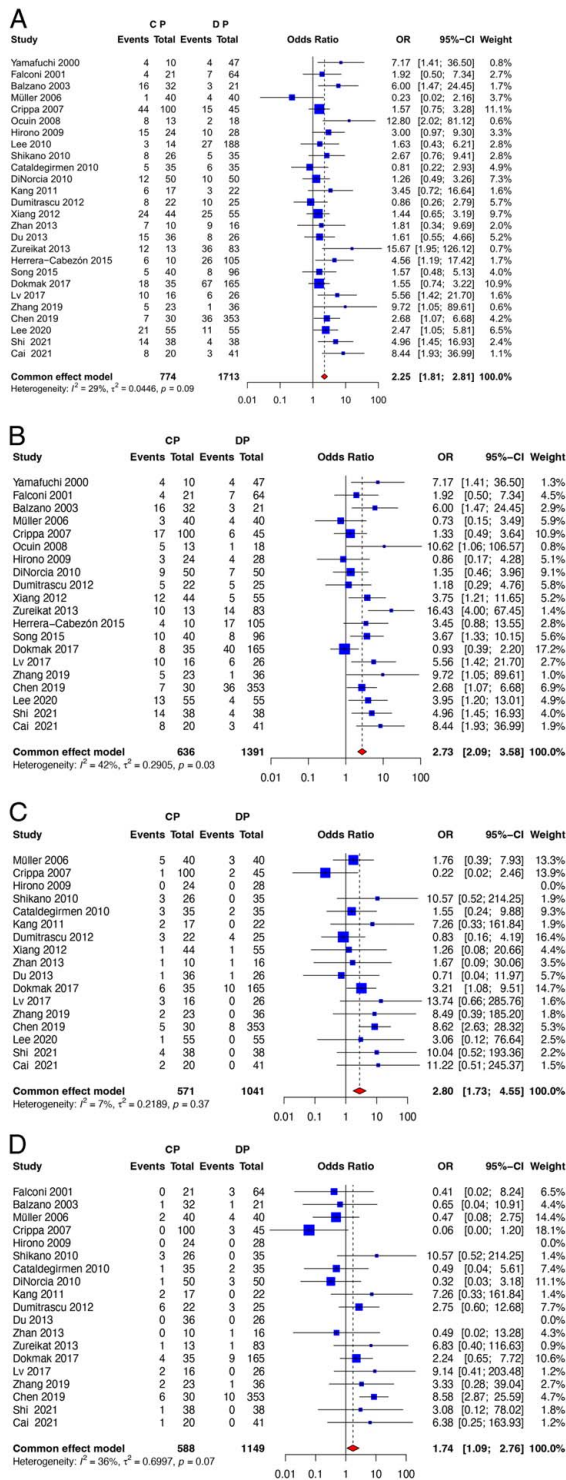
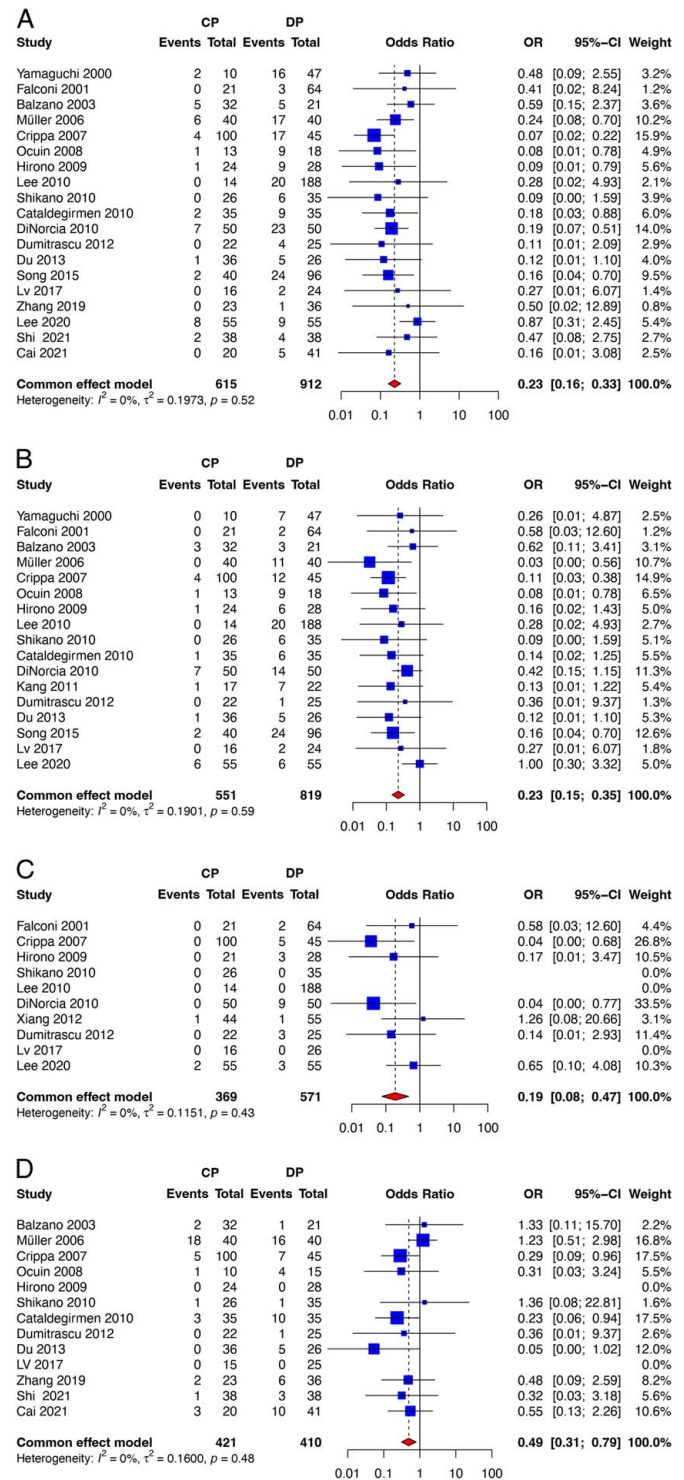


Figure 3. Forest plots of meta-analysis. A pancreatic fistula; B Clinically relevant pancreatic fistula; C POH; D reoperation.

Long-term outcomes

The postoperative overall rate of endocrine insufficiency was observed in 19 studies. The CP group ($n = 41$, 6.7%) had a lower occurrence of endocrine insufficiency than the DP group ($n = 188$,



rates of worsening diabetes mellitus were observed in the CP group ($n = 3$, 0.8%) than in the DP group ($n = 26$, 4.6%) (OR: 0.19; 95% CI: 0.08–0.47; $P < 0.0001$) (Fig. 4C). Data on postoperative exocrine function insufficiency were reported in thirteen studies. The DP group ($n = 64$, 15.6%) was more prone to exocrine insufficiency than the CP group ($n = 36$, 8.6%) (OR: 0.49; 95% CI: 0.31–0.79; $P = 0.003$) (Fig. 4D). Data on tumor recurrence were obtained from 10 studies, and the results of a meta-analysis of CP versus DP tumor recurrence rates showed no statistical difference (OR: 1.52; 95% CI: 0.65–3.52; $P = 0.3336$) (Supplementary Fig. 2c, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Sensitivity analyses and subgroup analyses

In the case of statistical heterogeneity, we performed sensitivity analyses for surgical outcomes by evaluating differences in the outcomes and significance using fixed and random effects models for the meta-analysis. I^2 was used to rank the variation in heterogeneity as follows: less than 40% low; 40–60% moderate; and greater than 60% high heterogeneity. Intraoperative blood transfusions showed low heterogeneity (Table 2).

However, a high degree of heterogeneity was found between the two variables (operative time and blood loss), and we divided the study into two subgroups: open or minimally invasive and prospective or nonprospective. However, we did not identify significant sources of heterogeneity for any of the parameters. This could be due to the differences in surgical experience between operators and the learning curve of CP.

In terms of postoperative short-term outcomes, subgroup analyses were performed based on the surgical approach including open as well as minimally invasive. We found no statistically significant differences between the two subgroups in the incidence of PF, clinically relevant PF, POH, reoperation, morbidity, severe morbidity, and LOS. Our results are supported by Huynh and Farrarons, who conducted a single-center study and meta-analysis of postoperative complications after open surgery and minimally invasive pancreatectomy, respectively^[44,45]. Regarding DGE and intra-abdominal abscess or effusion we found that open surgery may increase the incidence of DGE and minimally invasive surgery may increase the incidence of abdominal abscesses (Supplementary materials, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>). In the above analysis, only conclusions were drawn on top of the existing ones due to the limitation on the number of studies now, and more articles may be needed in the future to conduct subgroup analysis to draw conclusions to confirm. Finally, sensitivity analyses were required, and after excluding each study, the effect sizes for the remaining included studies did not change significantly, suggesting that the results of this analysis are robust and reliable (Supplementary materials, Supplemental Digital Content 5, <http://links.lww.com/JS9/A694>).

Publication bias

Funnel plot and Egger's test were used to test for publication bias for the surgical outcomes included in this study and $P < 0.05$ indicated publication bias. In this meta-analysis, publication bias may have existed in postoperative PF (Fig. 5A), hospital stay (Fig. 5B), and morbidity (Fig. 5C) (Egger's tests are shown in Table 2). The causes of funnel plot asymmetry include citation bias, true heterogeneity, selectivity bias, language bias, and

publication bias. Therefore, for the above three outcomes, we used a contour-enhanced funnel plot combined with a trim-and-fill method to determine whether the asymmetry in the funnel plot was due to publication bias. The results suggested that most of the missing studies were distributed within the white areas, indicating that the asymmetry in the funnel plot was due to publication bias. As for the other outcomes, the funnel plot suggested basic symmetry, and the tests showed no significant publication.

Discussion

For benign and low-grade malignant masses localized in the head or neck of the pancreas, DP is used more commonly than CP. This meta-analysis included studies up to February 2022, excluding those with small sample sizes and a poor representation, to reduce heterogeneity and make the surgical outcomes more meaningful. We included high-quality studies based on the NOS (Table 1)^[46]. Although most of the studies included here were retrospective studies, in terms of the level of evidence, a paper published in 2010 showed that well-designed nonrandomized controlled trials were as accurate as randomized controlled trials^[47].

The most recent meta-analysis of DP and CP was published in 2020, which included 24 studies and a total of 1819 patients (CP = 593, DP = 1226)^[18]. This concluded that CP better protected the function of the pancreas, but was associated with longer operative times, longer hospital stays, higher PF rates, and a higher overall postoperative complication rate. However, this meta-analysis excluded several studies and included few patients in the CP group, resulting in some common postoperative outcomes such as DGE, reoperation, and intraoperative blood loss, for which no statistical significance was observed.

EN, first reported in 1960^[48], is also indicated for benign or low-grade malignant masses localized in the pancreas. However, the inclusion criteria are narrower than those for CP. Current surgical principles suggest that EN is only suitable for tumors less than 2 cm in diameter and that the distance between the tumor and the main pancreatic duct needs to be greater than 3 mm, making it suitable for superficial tumors that do not involve the main pancreatic duct. Although this has not been validated in large clinical trials, the evidence from small sample data studies is not sufficiently convincing^[9]. In meta-analyses assessing EN versus pancreatic resection, EN had some advantages in terms of operative time, intraoperative blood loss, and POPF^[49,50] and better protected against pancreatic endocrine dysfunction. However, EN damage to the main pancreatic duct remains a concern.

This study showed that the CP group had a significantly longer operative time than the DP group. It is expected because the CP procedure requires digestive tract reconstruction^[11], which can take a significant amount of time. In terms of intraoperative blood transfusion, the conclusions of this study align with those obtained from three previous studies^[14,17,18], with no statistically significant differences ($P = 0.0999$). In terms of intraoperative blood loss, the conclusions drawn from this study appear to be consistent with the findings of previously published meta-analyses^[15,16,18], with the CP group losing less blood intraoperatively than the DP group and was statistically significant ($P < 0.01$). All meta-analyses showed high heterogeneity in terms of blood transfusion and duration of surgery, and further studies are needed to confirm this.

For procedures involving pancreatic resection, PF is always among the most common and prognostic complication, and the

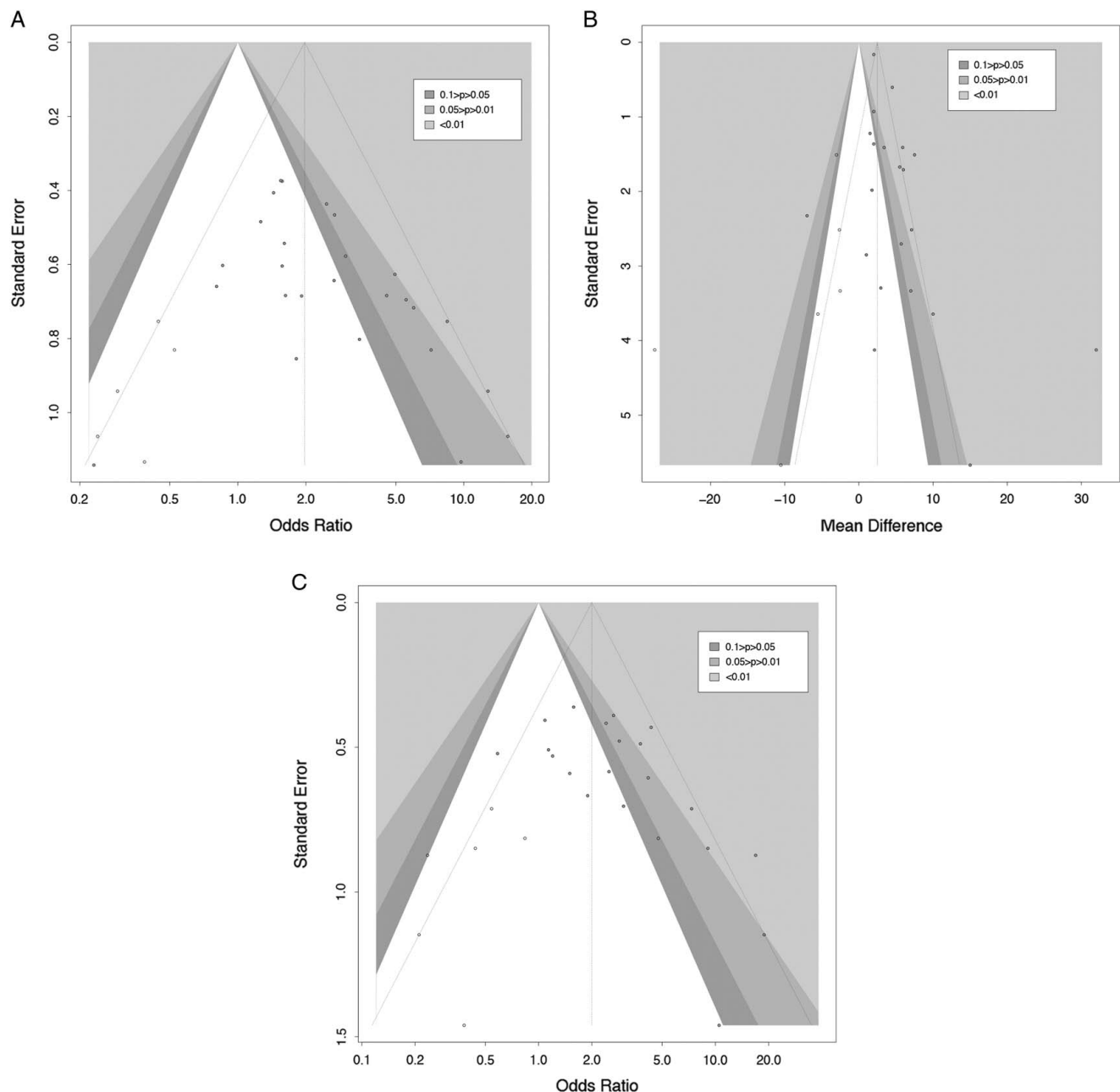


Figure 5. Funnel plots. A, pancreatic fistula; B, LOS; C, morbidity.

incidence of pancreatic leakage after surgery has been reported to be 3–40%^[51,52]. In this meta-analysis, we mainly focused on clinically relevant pancreatic leaks, that is, grades B and C, than in the overall incidence of pancreatic leaks. Twenty of the 26 publications reported the incidence of clinically relevant pancreatic leaks, and the results showed that the incidence of clinically relevant pancreatic leaks was significantly higher in the CP group than in the DP group ($P < 0.0001$). Three of the five previous meta-analyses reported the incidence^[14,17,18], but one suggested that it was not statistically significant^[14]. And some studies have shown a high incidence of intra-abdominal effusion or abscess in patients with pancreatic leaks^[53,54]. Ten studies were included to compare the incidence of peritoneal effusion or abscess in

patients, and the results showed that patients in the CP group had a higher incidence of peritoneal effusion or abscess than those in the DP group ($P = 0.0161$).

In terms of postoperative DGE, only one of the five meta-studies^[17] performed a correlation analysis, and the results suggested that no significant differences were found. In contrast, in this study, the probability of DGE after CP was higher than that after DP ($P = 0.0096$). Studies have shown that the incidence of DGE can reach 5–40% in pancreatic resection, moderate to severe PF is an independent risk factor for secondary DGE, and other abdominal complications likewise increase the incidence of DGE^[55–57]. Therefore, abdominal complications control can reduce the occurrence of DGE. The current meta-analysis

suggested that POH was significantly higher in the CP group than in the DP group ($P < 0.0001$). POH is also a serious and common complication after pancreatic resection, and can be divided into early and late bleeding according to the time of occurrence, with early bleeding mostly due to inaccurate hemostasis or poorly ligated vascular dissection^[58]. Late POH, although rare, is a very worrying sequela of POPF. Most commonly, it involves the development of pseudoaneurysms in the visceral arteries and their rupture during hemodynamic instability due to prolonged contact of the intra-abdominal vessels with pancreatic fluid containing high amounts of proteases^[59].

The incidence of reoperation was documented in 19 of 26 studies, and the present study suggests that the incidence of reoperation was significantly higher in the CP group than in the DP group ($P = 0.0196$). These results were inconsistent with two meta-analyses published in 2013^[14,15] and with the same conclusions as these three meta-analysis studies^[16–18], although these were not statistically different.

LOS was reported in 21 of the 26 studies, and our results showed that patients in the CP group, on average, were hospitalized for longer than those in the DP group ($P = 0.0002$). Length of hospitalization increased due to the complex nature of CP compared to DP surgeries.

Overall, postoperative complications were significantly more common in the CP than the DP group, and this outcome was the same as the previous meta-analysis outcome, and both were statistically significant. Most complications occur due to a chain reaction triggered by pancreatic leakage; therefore, it is crucial to reduce the incidence of PF following CP surgery^[53,54,57,59].

Exocrine and endocrine insufficiencies, long-term postoperative complications, were significantly less common in the CP group than those in the DP group. The incidence of NODM and the rate of worsening diabetes were significantly lower in the CP group than in the DP group. We preferentially used the incidence of NODM and worsening diabetes as indicators of endocrine function^[60]. CP surgery can improve the patient's long-term quality of life by maximizing the preservation of normal tissue. The relevant literature reported that for benign masses, the incidence of NODM exocrine insufficiency after PD surgery reached 14–41%^[61,62]. The incidence of NODM after DP surgery was 12.6–30.2% and the incidence of exocrine insufficiency was 20.2%^[60,63]. Together, these data suggest that CP is recommended for patients who meet the surgery's inclusion criteria. In this study, the two main methods of reconstructing the distal pancreatic stump with the digestive tract were summarized in Table 3.

Pancreaticojejunostomy (PJ) was performed in 61.0% (397/651) of patients and pancreaticogastrostomy (PG) in 35.6% (232/651) of patients. In recent years, the effects of PG and PJ on the incidence of POPF after PD has been controversial. Some studies suggested that the overall incidences of PF and clinically relevant PF were lower in the PG group than in the PJ group^[64,65]. A meta-analysis by Crippa *et al.*^[66] in 2016 did not demonstrate the superiority of pancreaticogastric anastomosis. The study showed no significant difference between the incidence of overall PF and that of clinically relevant PF. The heterogeneities in these studies may be due to the different diagnostic criteria for POPF, as well as inconsistent anastomotic techniques used in different centers and inconsistent perioperative management. Ricci *et al.*^[67] performed a meta-analysis of seven prospective randomized controlled studies on the effect of PJ versus PG on POPF,

controlling for heterogeneity. They showed that PG was superior to PJ in terms of PF occurrence. Therefore, PJ may increase the risk of POPF after CP.

In summary, our study showed that most short-term complications of this procedure were significantly higher than those of DP. Although DP had a higher incidence of long-term postoperative endocrine and exocrine insufficiency, this was well controlled by oral hypoglycemic agents, insulin, and pancreatic enzymes^[68,69]. The main objective of CP is to preserve more normal pancreatic tissues to better protect the secretory function of the pancreas. CP is considered an ideal procedure for benign or low-grade malignant tumors (less than 5 cm in diameter) located in the neck and proximal body of the pancreas. The high incidence of short-term complications after CP, on the other hand, especially POPF, remains a challenge. It has been showed that patient related risk factors such as age (> 70 years), sex (male), BMI greater than 25 or pancreas anatomic related factors such as pancreatic disease, pancreatic softness, pancreatic duct diameter less than or equal to 3 mm or procedure related factors such as anastomosis of residual pancreas digestive tract, and surgeon experience were risk factors for PF after PD^[70–72]. The selection of a surgical approach also needs to take the pathological type into account. Although CP can be used for neuroendocrine neoplasms, serous cystadenoma, and intraductal papillary mucinous neoplasms. It had been shown that patients with main-duct IPMN have a high rate of positive margin and recurrence^[8]. Therefore, DP currently has greater clinical applicability.

Of course, there are some limitations in this article. First, the included studies were retrospective design. Patient selection bias and receipt collection bias would be unavoidable. Secondly, the diagnostic criteria of complications vary considerably among the reviewed articles. Lastly, the limited number of the included studies, with limited sample size, might compromise the power of the statistical inference.

Conclusion

CP cannot yet be routinely recommended for benign or low-grade malignant lesions occurring in the neck of the pancreas as well as in the proximal body. It should be considered as an alternative to DP in selected cases such as without pancreatic disease, length of the residual distal pancreas greater than or equal to 5 cm, branch-duct intraductal papillary mucinous neoplasms, and a low risk of POPF after adequate evaluation. Considering the surgical skills and treatment experience, the indications for CP should be broadened in center with a high volume case load.

Ethical approval

This meta-analysis has no ethical approval.

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Author contribution

S.B.: contributed to the conception of the study, literature research and manuscript preparation; Y.L., W.D., L.P., S.Y., and Y.Z.: contributed significantly to data acquisition; S.W., J.K.: helped perform the analysis with constructive discussions.

Conflicts of interest disclosure

Shiyuan Bi, Yingyu Liu, Wanlin Dai, Liwei Pang, Shaojie Yang, Yuting Zheng, Xiaolin Zhang, Shudong Wu, Jing Kong declare that they have no conflict of interest.

Research Registration Unique Identifying Number (UIN)

1. Name of the registry: Effectiveness and safety of central pancreatectomy in benign or low-grade malignant pancreatic body lesions: A systematic review and meta-analysis.
2. Unique Identifying number or registration ID: Review-registry1471.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmetaanalyses/registryofsystematicreviewsmetaanalysesdetails/63637ec1f98407002397246b/>.

Guarantor

Dr Shiyuan Bi and Prof. Jing Kong are the guarantor.

Data availability statement

All data for this paper were obtained from the 26 original papers included. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

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