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Radicality and safety of total mesopancreatic excision in pancreatoduodenectomy: a systematic review and meta-analysis



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Abstract

Background Pancreatic head cancer patients who undergo pancreatoduodenectomy (PD) often experience disease recurrence, frequently associated with a positive margin status (R1). Total mesopancreas excision (TMpE) has emerged as a potential approach to increase surgical radicality and minimize locoregional recurrence. However, its effectiveness and safety remain under evaluation.

Methods We conducted a systematic review and meta-analysis to synthesize current evidence on TMpE outcomes. A systematic search of MEDLINE, EMBASE, Cochrane, and Web of Science databases was conducted up to March 2024 to identify studies comparing TMpE with standard pancreatoduodenectomy (sPD). The risk ratio (RR) or mean difference (MD) was pooled using a random effects model.

Results From 452 studies identified, 9 studies with a total of 738 patients were included, with 361 (49%) undergoing TMpE. TMpE significantly improved the R0 resection rate (RR 1.24; 95% CI 1.11–1.38; P < 0.05), reduced blood loss (MD -143.70 ml; 95% CI -247.92, -39.49; P < 0.05), and increased lymph node harvest (MD 7.27 nodes; 95% CI 4.81, 9.73; P < 0.05). No significant differences were observed in hospital stay, postoperative complications, or mortality between TMpE and sPD. TMpE also significantly reduced overall recurrence (RR 0.53; 95% CI 0.35–0.81; P < 0.05) and local recurrence (RR 0.39; 95% CI 0.24–0.63; P < 0.05). Additionally, the risk of pancreatic fistula was lower in the TMpE group (RR 0.66; 95% CI 0.52–0.85; P < 0.05).

Conclusion Total mesopancreas excision significantly increases the R0 resection rate and reduces locoregional recurrence while maintaining an acceptable safety profile when compared with standard pancreatoduodenectomy. Further prospective randomized studies are warranted to determine the optimal surgical approach for total mesopancreatic resection.

Keywords Pancreatoduodenectomy, Mesopancreas, Total mesopancreas excision, Meta-analysis, Systematic review

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Introduction

Pancreatic cancer is the seventh leading cause of cancer death worldwide, accounting for almost as many deaths annually as new cases, and its increasing incidence is attributed to rising risk factors such as obesity, diabetes, and alcohol consumption [1-3]. Currently, surgery is the cornerstone and curative option for treating pancreatic adenocarcinoma (PDAC), aiming for margin-negative resection (R0) [4–6]. However, even patients undergoing curative treatment exhibit high recurrence rates ranging from 59.7 to 91.1%, which has been associated with a positive margin status (R1) [7, 8]. Since its initial description in the early 20th century, pancreatoduodenectomy (PD), the standard surgical approach for treating PDAC located in the head of the pancreas, has undergone numerous modifications to improve oncological outcomes [9-12]. Although advancements in surgical techniques and the development of minimally invasive approaches have been made, achieving R0 resection remains limited to less than 50% of patients with PDAC [13]. Furthermore, aggressive extended resection aimed at improving resectability and radicality (R0 resection rates) has shown no survival benefits in clinical trials, encompassing paraaortic lymph node dissection and superior mesenteric artery (SMA) nerve plexus dissection for PDAC in the pancreatic head [14, 15].

Within this context, total mesopancreas excision (TMpE), coupled with circumferential lymphadenectomy, has emerged as a potential approach to minimize R1 resection and locoregional recurrence [16–18]. The mesopancreas, alternatively referred to as the "pancreatic head plexus", "retroportal lamina" or "mesopancreatoduodenum", encompasses retropancreatic tissue, including adipose tissue, peripheral nerves and plexuses, and vascular structures, constituting a controversial and debated anatomical entity [19–21]. The mesopancreatic resection margin, yielding the retroperitoneal, uncinate, posterior, and portal vein groove margins, has been identified as the primary site for R1 resection due to neoplastic invasion of neurovascular and lymphatic tissues [22-25]. Therefore, total mesopancreatic excision ("en bloc mesopancreatic resection") has been suggested to increase the clearance of peripancreatic retroperitoneal tissue, improving oncological outcomes [26, 27].

Currently, there is limited evidence regarding the effectiveness and safety of total mesopancreatic excision (TMpE), compounded by a lack of randomized controlled trials. Therefore, we conducted a systematic review and meta-analysis to comprehensively assess the oncological outcomes associated with TMpE and to determine whether increased radicality is accompanied by manageable postoperative complications.

Materials and methods

This systematic review and meta-analysis were performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [28]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024551679).

Search strategy and selection criteria

A systematic digital search was conducted across the MEDLINE, EMBASE, Cochrane (CENTRAL) and Web of Science databases up to March 2023. The search utilized terms related to mesopancreatic excision: "Meso-Pancreatoduodenum" OR "Mesopancreatoduodenum" OR "Mesopancreas" OR "Retroportal lamina" OR "Retropancreatic lamina" OR "Mesopancreatic excision" OR "Mesopancreas excision" OR "pancreatic head plexus". The references from all included studies and previous systematic reviews were also searched manually for any additional studies. Two investigators (L.F. and J.S.) independently reviewed the titles and abstracts for eligibility and discussed them with a senior investigator in case of disagreement. The full text, supplementary material, online appendices, and reference lists of each eligible study were examined to confirm adherence to the inclusion criteria and to identify any additional relevant studies. Any disagreements were resolved through discussion with other reviewers to achieve consensus.

The inclusion criteria in this systematic review were restricted to studies that met all the following eligibility criteria: (1) were randomized trials or nonrandomized cohorts; (2) compared total mesopancreatic excision ("en bloc resection") with sPD; and (3) enrolled patients with PDAC who underwent pancreatoduodenectomy (Whipple procedure). In addition, studies were included only if they reported any of the clinical outcomes of interest. We excluded studies with (1) no control group; (2) case reports, literature reviews, editorials, comments, or letters; or (3) available only in the abstract format.

Data extraction and quality assessment

A comprehensive data extraction process was implemented, covering the number of patients, median age, body mass index (BMI), ASA score, mesopancreatic definition, and surgical technique. The oncological outcomes were the achievement of R0 margins, number of lymph nodes harvested (LNH), locoregional recurrence, and disease-free survival (DFS). Surgical outcomes included procedure duration and length of hospitalization. Postoperative pancreatic fistula (POPF) was defined according to the International Study Group on Pancreatic Fistula [29], and adverse events were classified using the Clavien-Dindo grading system [30]. The Newcastle-Ottawa Scale [31] (NOS) was used in this meta-analysis to evaluate the quality of nonrandomized trials. This scale includes Representativeness of the Exposed Cohort, Selection of the Non-Exposed Cohort, Ascertainment of Exposure, Outcome Not Present at Start, Assessment of Outcome, Adequate Follow-Up Length, and Adequacy of Follow-Up. Scores were classified as follows: 7–9 indicated a low risk of bias, 4–6 indicated a moderate risk, and scores below 4 indicated a high risk of bias.

Statistical analysis and data synthesis

The risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model to compare treatment effects for categorical endpoints. Pooled mean differences (MDs) were employed to synthesize data regarding continuous endpoints. The Cochran Q test and I2 statistics were used to assess heterogeneity; P values less than 0.10 and I2>25% were considered significant for heterogeneity [32]. When necessary, means were estimated from medians and interquartile intervals with the method described by Luo et al. [33]. A leave-one-out sensitivity analysis was performed to evaluate the influence of individual studies on the overall results of the metaanalysis [34]. Furthermore, the extracted data from the studies were systematically organized into data tables and graphics and were critically reviewed. Review Manager 5.4 (Cochrane Centre, The Cochrane Collaboration, Denmark) and R-studio were used for statistical analysis. Publication bias was investigated by funnel plot analysis of point estimates according to study weights. Egger's test was used to assess funnel plot asymmetry by performing a linear regression of the log risk ratio against the inverse standard error [35].

Results

Baseline characteristics of cohorts evaluating TMpE

We identified 452 studies through a database search strategy. After excluding duplicates and unrelated studies, 149 studies were fully evaluated. Overall, 738 patients were included from 9 studies, 361 (49%) of whom underwent mesopancreatic resection. The characteristics of the included studies are detailed in Table 1. Overlapping cohorts were identified between Kawabata 2012 and Kawabata 2016 [22, 38], as well as between Quero 2020 and Quero 2021 [36, 37], and a sensitivity analysis encompassing those with longer follow-up periods was performed. The study designs ranged from two studies with propensity score matching [36, 37] but overlapping populations, one prospective cohort study [26] and six retrospective studies [22, 38–41, 42]; Table 2.

Baseline characteristics, including median age, number of patients and sex, were presented proportionally between TMpE and control group across all studies (Table 1). No neoadjuvant therapy was reported for any patient. Furthermore, studies that described the tumor size (mm) and of ASA Score presented similar values for patients undergoing TMpE and sPD. Nevertheless, some studies had a subtle disproportion between treatment groups regarding TNM staging, as a higher proportion of TNM stage II patients in the control group in Kawabata et al. [38], and a higher number of stage III patients in Kawabata et al. [22]; (Table S2). These subtle baseline differences could contribute to observed heterogeneity in the outcomes. Mesopancreas definition presented similar aspects across studies, encompassing blood vessels, lymphogenic structures, nerve fibers and locoregional lymph nodes posterior to pancreas (Table S2; Fig. 1).

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First Author/Year	Country	Study Design	Inclusion Period	Number of patients	Age (median)	Fe- male (%)	Neoad- juvant therapy (%)	Tumor size (mm)	ASA≥3 (%)
Quero, [37]*	Italy	PSM	2004-2013	60/60	64/64	47/52	0/0	27(±12)/25(±13)	8/10
Du, [41]	China	Retrospective	2015-2016	28/32	57/55	43/40	N/A	N/A	N/A
Quero, [<mark>36</mark>]*	Italy	PSM	2004-2019	37/37	64/64**	59/49	0/0	21(±8.5)/20(±11)	7/5
Xu, [<mark>36</mark>]	China	Prospective	2013-2015	58/43	63/63**	31/46	0/0	36(±15)/34(±15)	5/5
Kawabata, [<mark>38</mark>]*	Japan	Retrospective	2006-2011	14/25	72/73	71	N/A ^A	N/A	N/A
lnou e, [<mark>42</mark>]	Japan	Retrospective	2006-2010	82/80	67/66**	44/38	N/A	N/A	N/A
Aimoto, [<mark>40</mark>]	Japan	Retrospective	2009-2012	19/19	70/67**	37/45	0/0	N/A	N/A
Shrestha, [39]	Nepal	Retrospective	2018-2021	30/40	56/53	56/53	N/A	20(20)/24(26) ^B	N/A
Kawabata, [22]*	Japan	Retrospective	2003-2015	33/41	72/72	36/39	N/A	N/A	N/A

Baseline characteristics of the included studies. Data are presented in the format of patients who underwent TMpE/sPD

*Studies with overlapping cohorts

**These values refer to mean age; PSM: propensity score-matched studies

^APatients with tumor invasion to the superior mesenteric artery (SMA) or extrapancreatic nerve plexus (PL) without distant metastasis underwent neoadjuvant chemoradiotherapy

^BThese values refer to median (IQR)

Table 2	Comparison of	foutcomes betwee	n mesopancreatic excisio	n and standard	pancreatoduodenectomy
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Outcomes	No. of studies	No. of patients	Risk ratio or *mean difference (TMpE versus sPD)	Р	I2 (%)
Blood loss (ml)	7	630	-143.70 [-247.92, -39.49]*	< 0.05	91%
Duration of operation (min)	7	630	-6.86 [-29.69, 15.97]*	0.56	68%
Postoperative mortality	4	526	0.64 [0.23; 1.82]	0.40	0%
Postoperative complications	6	432	1.07 [0.86; 1.33]	0.55	17%
Clavien–Dindo grade≥III complications	4	426	0.82 [0.56; 1.19]	0.29	0%
Pancreatic fistula	8	668	0.66 [0.52; 0.85]	< 0.05	0%
Fístula grade A	5	469	0.87 [0.52; 1.44]	0.58	24%
Fístula grade B/C	5	469	0.39 [0.18; 0.81]	< 0.05	42%
R0 resection	5	312	1.24 [1.11; 1.38]	< 0.05	0%
Duration of hospital stay (days)	6	570	-6.13 [-12.28; 0.03]*	0.05	70%
Lymph node harvested	5	408	7.27 [4.81; 9.73]*	< 0.05	85%
Adjuvant chemotherapy	3	208	1.18 [0.83; 1.66]	0.36	75%
Diarrhea	6	397	1.59 [0.95; 2.66]	0.08	0%
Delayed gastric emptying	6	443	0.64 [0.40; 1.04]	0.07	16%
Local recurrence	5	397	0.39 [0.24; 0.63]	< 0.05	0%
Recurrence rate	6	458	0.53 [0.35; 0.81]	< 0.05	48%
Reoperation	4	306	0.74 [0.29; 1.90]	0.53	0%

The values in parentheses are the 95% CIs; TMpE: total mesopancreatic excision; sPD: standard pancreatoduodenectomy. A negative MD indicates a benefit of TMpE over sPD. Risk ratios less than 1 indicate a benefit of TMpE over sPD





Fig. 1 PRISMA flow chart. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for literature search and selection; n: number of patients

Surgical and oncological outcomes related to TMpE compared to those related to standard PD

The R0 resection rate was significantly greater in the TMpE group than in the standard pancreatoduodenectomy (sPD) group (RR 1.24; 95% CI 1.11-1.38; P<0.05; Fig. 2A). The mean difference in blood loss was significantly lower in the TMpE group than in the sPD group (MD -143.70 ml; 95% CI -247.92, -39.49; P<0.05). The average number of lymph nodes harvested was significantly greater in the TMpE group (MD 7.27 nodes; 95% CI 4.81, 9.73; P<0.05; Fig. 2C). No significant differences were detected between the groups for hospital stay (MD -6.13 days; 95% CI -12.28, 0.03; P=0.05), postoperative complications (RR 1.07; 95% CI 0.86-1.33; P=0.55), or postoperative mortality (RR 0.64; 95% CI 0.23-1.82; P=0.40). There was no significant difference in the reoperation rate between the two groups (RR 0.74; 95% CI 0.29–1.90; *P*=0.40) or in the operative time (MD -6.86 min; 95% CI 0.29.69, 15.97; P=0.56)

The recurrence and local recurrence rates were significantly lower in the TMpE group than in the sPD group (RR 0.53; 95% CI 0.35–0.81; P<0.05, Fig. 2B) and (RR 0.39; 95% CI 0.24–0.63; P<0.05), respectively. No

significant difference was observed in the administration of adjuvant chemotherapy between the groups analyzed (RR 1.18; 95% CI 0.83–1.86; P=0.36). The exclusion of studies with overlapping cohorts yielded consistent findings, with the risk of R0 resection remaining significantly elevated (RR 1.21; 95% CI 1.08–1.36; P<0.05). A sensitivity analysis removing studies with overlapping populations for the outcomes of recurrence rate and local recurrence also demonstrated consistent results (supplementary files).

Safety of TMpE compared to sPD

The risk of pancreatic fistula was significantly lower in the TMpE group than in the sPD group (RR 0.66; 95% CI 0.52-0.85; P<0.05). There were no significant differences between the groups for the risk of complications classified as Clavien–Dindo≥III (RR 0.82; 95% CI 0.56–1.19; P=0.29), delayed gastric emptying (RR 0.64; 95% CI 0.40– 1.04; P=0.07, Fig. 3B) or diarrhea (RR 1.59; 95% CI 0.95– 2.66; P=0.08, Fig. 3C). Sensitivity analysis, employing the leave-one-out approach, revealed minimal fluctuations in risk ratios (RRs) upon exclusion of individual studies. For instance, in the pooled results regarding pancreatic



Fig. 2 Forest plots comparing TMpE with standard PD regarding the R0 resection rate, local recurrence rate and number of lymph nodes harvested. Forest plots of the risk ratios of (a) R0 resection, (b) local recurrence, and (c) number of lymph nodes harvested. Squares are the effect sizes of the individual studies; diamonds are the summarized effect sizes; horizontal lines are the upper and lower borders of the 95% confidence intervals; p values > 0.05 are considered to indicate statistical significance



Fig. 3 Forest plots comparing TMpE with standard PD regarding B/C pancreatic fistula, delayed gastric emptying and postoperative diarrhea. Forest plots of the risk ratios of (A) B/C pancreatic fistula, (B) delayed gastric emptying and (C) postoperative diarrhea. Squares are the effect sizes of the individual studies; diamonds are the summarized effect sizes; horizontal lines are the upper and lower borders of the 95% confidence intervals; p values > 0.05 are considered to indicate statistical significance

fistula, the RR ranged only from 0.63 to 0.69 across exclusions, with consistently low heterogeneity observed. Furthermore, a sensitivity analysis that removed studies with overlapping populations demonstrated results consistent with the main findings for pancreatic fistula outcome (RR 0.63; 95% CI 0.47–0.84; P<0.05).

Quality assessment and publication bias

The funnel plot exhibited a symmetrical distribution of studies, with comparable weights converging toward the pooled treatment effect size as study sizes increased. Due to the limited number of studies available for comparison, Egger's test was not applicable. Evaluation using the Newcastle–Ottawa assessment revealed that most studies demonstrated a low risk of bias. Nonetheless, some studies exhibited moderate bias, primarily attributed to the absence of statements regarding patient follow-up and inadequate reporting of essential baseline patient characteristics.

Discussion

In this systematic review and pooled analysis of 9 studies, we evaluated the efficacy and safety of total mesopancreatic excision in pancreatoduodenectomy. The key findings of our comprehensive analysis were as follows: (1) TMpE was associated with a greater rate of R0 resection and lymph node harvesting than was standard PD; (2) patients who underwent TMpE experienced a lower rate of locoregional recurrence, suggesting improved oncological outcomes; (3) the duration of surgery was similar between TMpE and sPD; and (4) TMpE was linked to a decreased risk of pancreatic fistula, and there were no significant differences in postoperative delayed gastric emptying between the groups. These findings suggest the efficacy of TMpE in achieving better oncological control while maintaining an adequate safety profile.

The term 'resection of mesopancreas' was first introduced by Gockel et al. as an analogy to the mesorectum and the technique of total mesorectal excision, which is known to increase local control after rectal cancer resection [18, 43, 44]. Positioned adjacent to major vascular structures such as the SMA, the mesopancreas harbors a critical neurovascular plexus and lymph nodes involved

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in the spread of pancreatic cancer [21, 45–47] Initial case series evaluating the results of TMpE revealed an R0 resection rate exceeding 60%, with mesopancreatic tumor invasion identified in the majority of cases [24, 26, 48].

In a propensity score-matched (PSM) study, Quero et al. compared 60 sPD patients to 60 PD patients with TMpE, which yielded more harvested lymph nodes (19.8 \pm 7.6 vs. 10.1 \pm 5.1; p<0.01), less local tumor recurrence (26.8% vs. 55.5%; p=0.002), and better disease-free survival (22.3% vs. 14.8%; p=0.04) with mesopancreatic excision [36]. Interestingly, in this PSM analysis TMpE was associated with a concomitant reduction of local (p=0.002) and distant (p=0.03) recurrence, while distant metastasis as the only site of recurrence were similar between groups. These findings are consistent with those of Aimoto et al. and Kawabata et al. [38, 40]. Our meta-analysis revealed a similar benefit of TMpE in terms of local recurrence and harvested lymph nodes.

Different surgical techniques have been evaluated to achieve surgical radicality and mesopancreatic resection [49]. Inoue et al. classified mesopancreatic dissection in PD patients into four levels. Level I is a standard approach without lymphadenectomy and is suitable for treating less aggressive pathologies, while level II involves 'en bloc' mesopancreas excision, lymphadenectomy, and soft tissue removal, which are suitable for treating tumors distant from the SMA and patients with compromised status. Level III entails removal of the nerve plexus around the pancreas head and hemicircumferential removal of the right and posterior nerve plexus around the SMA, while for tumors abutting the SMA up to 180° or more, extended level 3 involves complete circumferential removal of the periarterial plexus to ensure horizontal margins [42, 50]. Notably, the integration of these advancements in surgical techniques with minimally invasive approaches and robotic surgery has significantly contributed to improving outcomes in mesopancreatic resection, enhancing radicality and safety [51-53]. A prospective study evaluating the surgical feasibility of robotic TMpE revealed an increased R0 rate with level III resection compared with that with level II or I resection (93.8% vs. 72.2%, *p*<0.001) and decreased blood loss compared with that with open level III PD [54].

The 'triangle operation' approach was further explored for the excision of the mesopancreas, defining its anatomical boundaries as an inverted triangle with the apex at the origins of the celiac trunk (CT), hepatic artery, and SMA and the base at the posterior face of the superior mesenteric vein and portal vein [24, 55]. Another option that has been commonly adopted is the arteryfirst approach, which involves early control and dissection at the SMA margin at the initial stage of resection to identify arterial tumor infiltration, assess resectability, promote adequate clearance of the SMA, perform radical lymphadenectomy, and minimize bleeding by ligation of the inferior pancreaticoduodenal artery (IPDA) [56-58]. In fact, the optimal mesopancreatic excision surgical technique remains under evaluation. Mahmoud et al. conducted a study comparing the artery-first approach with the conventional 'triangle operation' for TMpE and concluded that both methods presented comparable operative times, blood loss and postoperative morbidity [59]. Furthermore, some studies have evaluated the incorporation of the Cattell-Braasch-Valdoni maneuver (intestinal derotation) to facilitate mesopancreatic resection, which seems to simplify the procedure anatomy and reduce the operative time [60-62]. Currently, there is an ongoing randomized controlled trial (MAPLE-PD trial) in which a mesenteric artery-first approach is compared with conventional TMpE [63].

Resectability is a crucial consideration in pancreatic surgery, but it must be balanced with surgical safety [50]. Mesopancreatic excision has been associated with an acceptable rate of pancreatic fistula, a critical complication of PD [26, 29, 64]. In the prospective cohort conducted by Xu et al., the rate of POPF was 30.2% in patients who underwent sPD, while the rate of POPF in patients who underwent TMpE was 25.9%. Our pooled results indicate a decreased risk of this complication with TMpE. These findings could be attributed to improved vascular resection with TMpE, which has been previously associated as a protective factor for POPF in metaanalysis [65, 66]. However, TMpE is associated with increased postoperative diarrhea in some studies, likely due to neuronal damage, and with a greater incidence in patients undergoing level III mesopancreatic excision [16, 54]. Severe or intractable diarrhea is a major postoperative concern in PD patients and is a possible cause of adjuvant chemotherapy failure, which is an important prognostic factor [67-69]. Notably, most patients who undergo TMpE have diarrhea controlled with antidiarrheal opioids, and studies have suggested that preemptive antidiarrheals effectively prevent intractable diarrhea [70]. Despite the risk of postoperative diarrhea, aggressive dissection of the nerve plexus may be justified for achieving optimal oncological outcomes. Furthermore, the TMpE technique did not increase the risk of perioperative bleeding, operative mortality, or hospitalization time.

Although our review provides valuable insights into the efficacy and safety of TMpE, it is important to acknowledge certain limitations. The heterogeneity among the included studies, such as variations in patient populations and surgical techniques, may have influenced the pooled results. To address this variability, a leave-oneout analysis was conducted to explore the impact of individual studies on pooled estimates. Additionally, the retrospective nature of the studies and the potential of selection bias should be considered in the interpretation. Furthermore, the limited availability of long-term follow-up data restricts the ability to assess the durability of oncological outcomes. The strengths of this review include the use of a systematic approach and the inclusion of a diverse range of studies to capture the available evidence. By synthesizing data from multiple studies, we were able to offer valuable insights into the comparative efficacy and safety of TMpE versus sPD. Furthermore, our review highlights the potential benefits of TMpE in achieving improved oncological outcomes, such as higher rates of R0 resection and lower locoregional recurrence rates, while also addressing the associated risks. Overall, these findings provide valuable guidance for surgeons in decision-making regarding surgical radicality in pancreatic cancer management, but further prospective randomized studies are warranted to determine the optimal surgical approach.

Conclusion

Total mesopancreas excision significantly increases the R0 resection rate and reduces locoregional recurrence while maintaining an acceptable safety profile when compared with standard pancreatoduodenectomy. Further prospective randomized studies are warranted to determine the optimal surgical approach for total mesopancreatic resection.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12957-024-03495-2.

Supplementary Material 1

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Author contributions

L.F.L.S. and M.B.O. contributed to the study concepts. The study design was developed by L.F.L.S. and J.S.A.M. Data acquisition was performed by L.F.C.A., L.H.P., and L.F.L.S. Quality control of data and algorithms was ensured by L.H.P. and L.F.C.A. Data analysis and interpretation were conducted by L.F.C.A. and L.F.L.S. L.F.C.A. also carried out the statistical analysis. Manuscript preparation was undertaken by L.F.L.S., L.F.C.A., J.S.A.M., and M.S.A. Manuscript editing was performed by L.F.L.S., M.B.O., ROA., and J.R. Finally, M.S.A., M.B.O., ROA., and J.R. reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable as this study is a systematic review and meta-analysis of previously published studies.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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