Pancreatoduodenectomy with Venous Resection or Palliative Therapy? A Meta-Analysis

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ABSTRACT

This review evaluated the risks and survival benefits of pancreatoduodenectomy associated with venous resection compared with palliative surgery. A systematic review with meta-analysis was performed. Higher overall survival was observed in the pancreatic resection group (HR = 4.000; 95% CI 2.800 to 5.200). However, the palliative group had fewer complications (RD = -0.170; 95% CI -0.260 to -0.070). There was no significant difference in the mortality rates (RD = 0.000; 95% CI -0.030 to 0.030). In centres with experience in pancreatic surgery, resection may be considered for locally advanced cancer and major venous invasion. Pancreaticoduodenectomy with vascular resection may improve survival for periampullary tumours compared with palliation therapy. However, pancreaticoduodenectomy with major venous resection has potentially higher morbidity than palliation therapy.

Key Words: *Pancreatoduodenectomy, Pancreatic neoplasms, Vascular surgical procedures.*

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INTRODUCTION

The incidence of ductal adenocarcinoma of the pancreas is increasing, and this type of tumour may become one of the main causes of malignancy-related death in the next decade.[1] This high mortality rate is due to its usual advanced presentation. Half of the patients have distant metastasis at the diagnosis, and only a minority of the tumours are considered resectable.[2] Pancreatic cancers present high biological aggressiveness, with early hematogenous dissemination.[3]

At present, the only curative option for periampullary tumours is the R0 surgical resection.[4,5] However, pancreatoduodenectomy for cancer is a technically complex procedure with a high risk for morbidity and mortality, especially when the tumour also involves the superior mesenteric/portal vein.[6,7] In high-volume institutions, the postoperative complications rates range from 35 to 44%,[8-12] and mortality rates range from 2.5 to 6%.[6,13,14] Even with curative-intent resection, the long-term survival is low.[15,16]

Although systemic dissemination remains an absolute contraindication to surgery, neoplasms with vascular involvement may benefit from vascular resection, offering a chance of cure given that the R0 surgery is achieved.[17,18]

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Many authors have proposed venous vascular resections in patients with periampullary neoplasms with an associated invasion of the portomesenteric venous axis.[19-22] However, the morbidity, mortality, and long-term survival outcomes for venous vascular resection are significantly worse than the standard pancreaticoduodenectomy.[16] Nevertheless, the survival gain of periampullary neoplasms associated with major venous resection compared with palliation therapy is still unknown.

This review aimed to compare the pancreatoduodenectomy associated with venous resection and palliative therapy (no resection) for treating patients with periampullary neoplasms.

METHODOLOGY

A systematic search was performed on Lilacs, Embase, Cochrane, Medline, Cochrane, and gray literature up to June 2022. The strategy comprised a combination of keywords and MeSH terms including mesenteric vein, vascular resection, portal vein, portal system, vein resection, vascular reconstruction, vein reconstruction, pancreas, pancreatic, neoplasm, cancer, tumour, adenocarcinoma, pancreaticoduodenectomy and duodenopancreatectomy. The protocol of this study was previously in a public database (PROSPERO: CRD42021292488).

Two independent authors performed literature search and screening. A third author resolved any disagreement. Any controlled observational or experimental study was considered for inclusion. Conference proceedings, editorials, animal models, letters, reviews, and case reports were excluded. There was no restriction for the search period and language. Inclusion criteria were studies comparing palliation therapy with pancreatoduodenectomy with major venous resection

(superior mesenteric vein, portal vein, or portomesenteric confluence) for periampullary tumour. Combined arterial resection was excluded. Robins-I was used to assess the bias and GRADEpro for certainty.[23,24]

The outcomes studied were overall survival, postoperative mortality, postoperative complications, bleeding, pancreatic leak, reoperation, and length of hospital stay.

The software STATA was used for statistical analysis. Categorical variables were described as risk difference (RD), and continuous variables were expressed as mean difference (MD). The hazard ratio (HR) was used for the evaluation of overall survival. If the HR was not informed, HR was estimated using previously published methods.[25-27] A fixed or random-effects analysis model was applied according to the I^2 statistics.[28] The level of significance was set at 0.05.

RESULTS

Initially, 1,487 papers were retrieved using the search criteria. After screening and applying eligibility criteria, ten studies were selected for the meta-analysis (Figure 1).[15,19,29-36] Only one study was a randomised prospective trial. The evaluation of the risk of bias is presented in Table I, and the certainty assessment is shown in Table II.

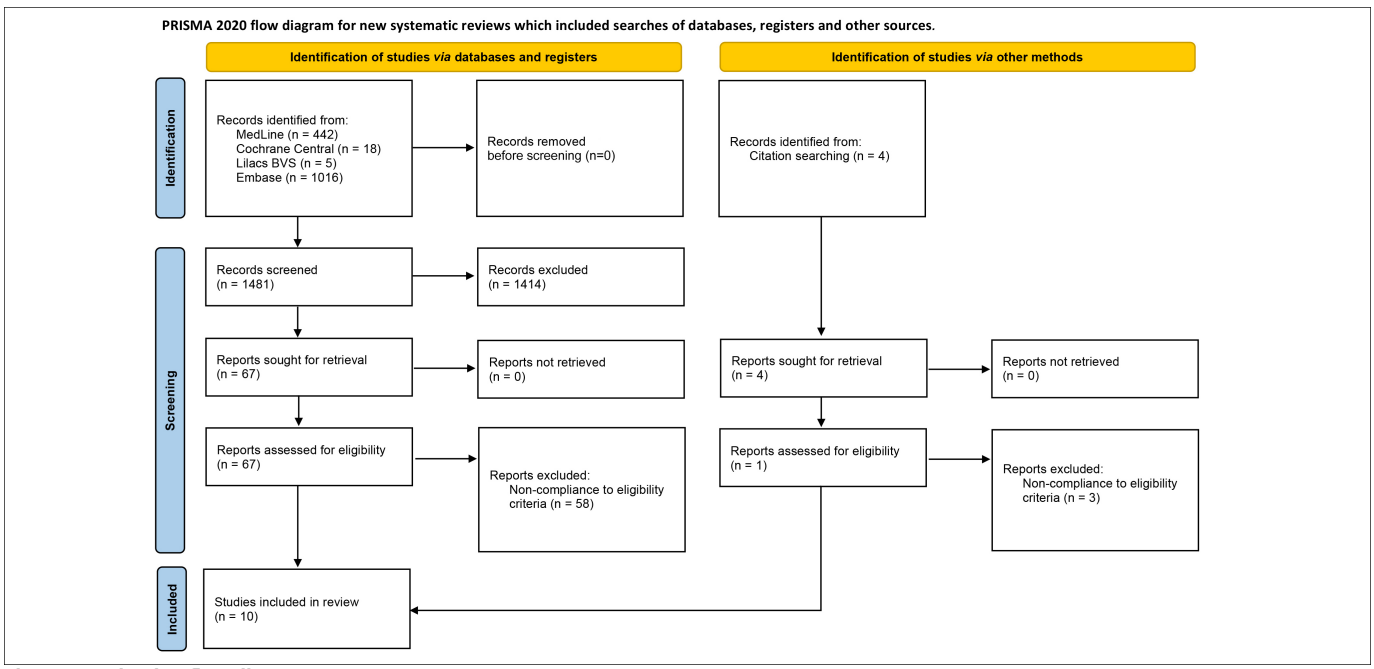

Figure 1: Selection flow diagram.

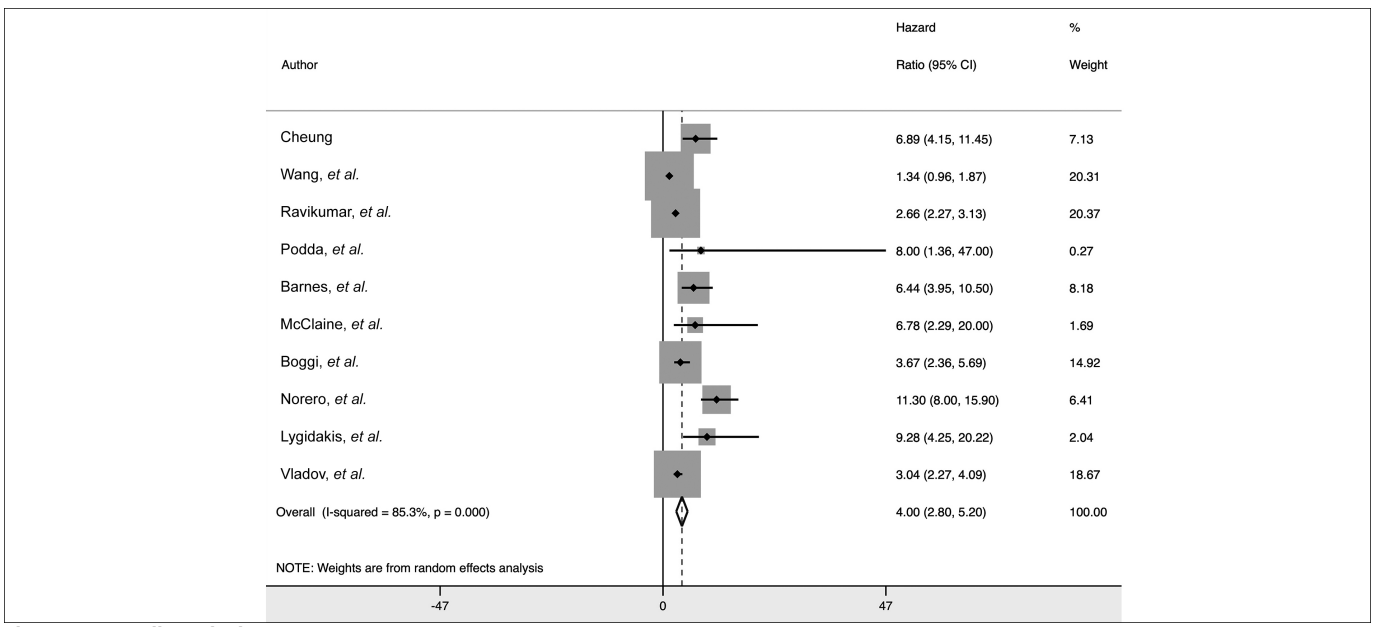

Figure 2: Overall survival.

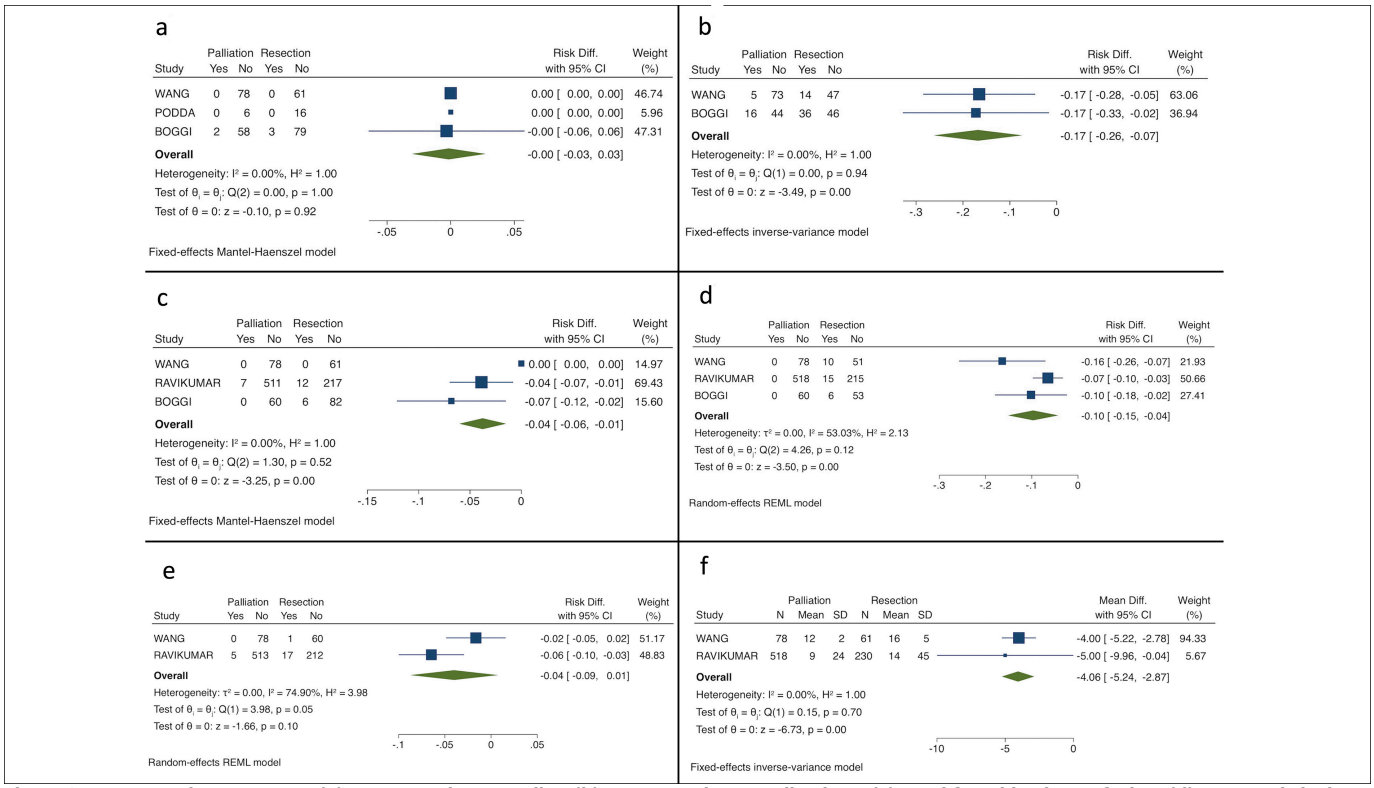

Figure 3: Postoperative outcomes. (a) Postoperative mortality; (b) Postoperative complications; (c) Need for a blood transfusion; (d) Pancreatic leak; (e) Reoperative procedures; (f) Length of hospital stay.

Table I: Analysis of the risk of bias (Robins-I).

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Cheung	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Wang, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Ravikumar, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Podda, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Barnes, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
McClaine, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Boggi, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Norero, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate
Lygidakis, *et al.*	Low	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Vladov, *et al.*	Low	Serious	Low	Low	Moderate	Moderate	Moderate	Moderate

Table II: Certainty assessment (GRADEpro).

Certainty assessment						
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**
Overall survival						
8 studies	Serious[a]	Serious[b]	Not serious	Not serious	None	⨁⨁◯◯ Low
Postoperative mortality						
3 studies	Serious[a]	Not serious	Not serious	Serious[c]	None	⨁⨁◯◯ Low
Postoperative complications						
2 studies	Serious[a]	Not serious	Not serious	Serious[c]	None	⨁⨁◯◯ Low
Bleeding						
3 studies	Serious[a]	Not serious	Not serious	Serious[c]	None	⨁⨁◯◯ Low
Pancreatic leak						
3 studies	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⨁◯◯◯ Very low
Reoperation						
2 studies	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⨁◯◯◯ Very low
Length of hospital stay						
2 studies	Serious[a]	Not serious	Not serious	Serious[c]	None	⨁⨁◯◯ Low

(a) Risk for selection bias; (b) Statistical heterogeneity I2 >50%; (c) Low-pooled sample size.

Table III: Included studies' main characteristics.

			Pancreatoduodenectomy associated with venous resection							Palliative surgery				
Author	**Year**	**Follow-up (months)**	**n**	**Male (%)**	**Tumour size (cm)**	**Mean age (yr)**	**Vein resection**	**Neoadjuvant therapy (%)**	**Serum CA 19.9**	**n**	**Male (%)**	**Tumour size (cm)**	**Mean age (yr)**	**Serum CA 19.9**
Cheung	2014	Up to 120	32	63	3	63	Portal vein	0	NI	46	54	3	67	NI
Wang, *et al.*	2008	Up to 60	61	62.3	NI	52	Portal vein, superior mesenteric vein, superior mesenteric-portal vein confluence	NI	NI	134	61.1	NI	53	NI
Ravikuma, *et al.*	2014	Up to 72	230	50	3	65	Portal vein, superior mesenteric vein	NI	NI	518	52.7	NI	64	NI
Podda, *et al.*	2017	46	16	NI	3.1	NI	Portal vein, superior mesenteric vein	0	NI	6	NI	NI	NI	NI
Barnes, *et al.*	2019	26	44	51	NI	64	Portal vein, superior mesenteric vein, superior mesenteric-portal vein confluence	93	350	11	51	NI	65	460
Mcclaine, *et al.*	2009	34	5	58	3.2	64.6	Portal vein, superior mesenteric vein, superior mesenteric-portal vein confluence	100	370	14	50	3.7	61.7	130
Boggi, *et al.*	2009	Up to 171	84	50	4.1	65.2	Portal vein, superior mesenteric vein, superior mesenteric-portal vein confluence	39	NI	62	56.4	NI	65.8	NI
Norero, *et al.*	2009	60	8	50	NI	58	Portal vein	NI	NI	NI	NI	NI	NI	NI
Lygidakis, *et al.*	2004	60	27	NI	NI	65	Superior mesenteric-portal vein confluence	NI	NI	27	NI	NI	67	NI
Vladov, *et al.*	2021	Up to 150	88	53.4	3.26	60.5	Portal vein, superior mesenteric vein, superior mesenteric-portal vein confluence	NI	NI	120	NI	NI	NI	NI

NI: Not informed.

One thousand, five hundred and thirty-three patients were included after selection. The study's mean age was 62.7 years. Male patients corresponded to 54.5%. The main characteristics of the included studies are depicted in Table III.

The studies followed the survivors up to at least 26 months. This difference in overall survival was statistically significant, with higher overall survival in the pancreatic resection group (HR = 4.00; 95% CI: 2.8 to 5.2; quality of evidence: low) as shown in Figure 2.

There was no difference in postoperative mortality rates (RD = 0.00; 95% CI : -0.03 to 0.03; quality of evidence: low, Figure 3a). The palliative group had fewer complications (RD = -0.17; 95% CI: -0.26 to -0.07; quality of evidence: low, Figure 3b).

Overall, the need for a blood transfusion rate was more frequent in the resection group (MD = -0.04; 95% CI: -0.06 to -0.01; quality of evidence: low, Figure 3c). As expected, the rate of the pancreatic leak was higher in the resection group (RD = -0.10; 95% CI: -0.15 to -0.04; quality of evidence: very low, Figure 3d). Like postoperative complications, the reoperation rate was higher after resection than after palliation (RD = -0.04; 95% CI: -0.09 to 0.01; quality of evidence: very low, Figure 3e).

The estimated difference in the length of total hospital stay (which included all patients' admissions related to the treatment) between the two groups favoured the palliative group (MD -4.06 days; 95% CI: -5.24 to -2.87; low quality of evidence, Figure 3f).

DISCUSSION

This systematic review showed that pancreatic resection increased survival in patients with locally advanced periampullary cancer as compared to palliative surgery. However, more extensive resection implied more significant morbidity, extended hospital stays, bleeding, and higher postoperative complications, including pancreatic leaks.

A previous meta-analysis showed that pancreatoduodenectomy with major vein resection was associated with a higher perioperative morbimortality and worse long-term results than without vascular procedures.[16] These findings raised the question whether pancreatoduodenectomy with major vein resection is the treatment of choice for local advanced periampullary neoplasms or whether palliation therapy should be applied; the results of the present systematic review have implications for decision-making. The higher long-term survival rate in the resection group compared with the palliation implies that pancreatoduodenectomy with vein resection should be the first-line therapy. However, knowing the higher perioperative morbidity of surgical resection, choosing between resection or palliation therapy should be based on an insightful patient clinical evaluation. Patient selection criteria should rely on age, performance status, and comorbidities, among other surgical risk variables.

In addition to evaluating surgical risk variables, the potential benefits and risks of performing resection or palliation therapy for advanced periampullary cancer should be shared with the patient and family. Shared decision-making (SDM) is a collaborative approach that involves the patient and their family, as well as the healthcare team, in the decision-making process. In SDM, the team provides the patient with information about their condition, the available treatment options, and the associated risks and benefits. The patient and their family are encouraged to ask questions and provide their preferences and concerns. In the context of complex conditions, such as locally advanced periampullary neoplasms, SDM can help ensure that the patient is well-informed about their options and is an active participant in the decision-making. The healthcare team can provide information about the surgical procedure, including the risks and benefits, and can discuss alternative treatment options, such as palliation therapy. The patient's preferences and values should be considered when making a decision. SDM can help to build trust between the patient and the healthcare team. When the patient feels heard and valued, there is a higher chance that the patient will be satisfied with the short and long-term surgical outcomes.[37]

The great gain in long-term survival with pancreatic and major venous resection is probably possible only when R0 resection is feasible. These procedures are complex and should only be performed in experienced centres so that the chance for R0 resection with low morbidity can be achieved.[38-45]

The resection of periampullary tumours with associated venous invasion of the portomesenteric axis has a high risk of overall morbidity, reoperations, and postoperative bleeding.[46] The mean operative mortality is 4%.[46] This high morbimortality could justify the augmented length of hospital stay in the resection group, which was observed in this study's results.

The present review also showed that the pancreatic leak is higher in pancreatic resection than in palliation therapy. The pancreatic leak could also contribute to the increased length of stay in the pancreatic resection group. Despite advances in preventing postoperative pancreatic leak in pancreatoduodenectomy,[47] the risk of this threatening complication still ranged between 3-45% of pancreaticobiliary resections, even in centres of excellence.[48-51] This complication was associated with higher morbidity, mortality, and length of hospital stay.[52] Conversely, the risk of a pancreatic leak was not added in palliative procedures (biliodigestive bypass or gastroenteroanastomosis).

This present study had several limitations. Only one study was a randomised clinical trial. Consequently, there was a significant risk of selection bias in the included studies when allocating patients to resection or palliation groups. The risk of selection bias contributed to the low certainty of the evidence for most outcomes. Also, there was high inter-study variability, including different surgical techniques, institutional experience across the studies, and neoadjuvant therapies. Currently, the therapy of choice for patients with invasion of the portomesenteric axis was neoadjuvant therapy followed by resection, and most of the included studies did not use neoadjuvant treatment. Future randomised controlled trials with standardised therapeutic protocols and chemotherapy regimens are needed to evaluate the safety and efficacy of pancreatoduodenectomy with major venous resection. Besides, new palliative treatments are available for treating periampullary cancer and should also be addressed in future studies.

CONCLUSION

In centres with experience in pancreatic surgery, resection may be considered for locally advanced cancer and major venous invasion. Pancreaticoduodenectomy with vascular resection may improve survival for periampullary tumours compared with palliation therapy. However, pancreatoduodenectomy with major venous resection has a potentially higher morbidity than palliation therapy.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
JELPF, SSBM: Search and selection.
ACH: Data extraction.
ARD, JW: Writing and supervision.
FT: Statistical analysis.
All authors approved the final version of the manuscript to be published.

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