

## Review Article

# Meta-analysis of pancreatic re-resection for locally recurrent pancreatic cancer following index pancreatectomy

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The role of surgical resection in patients with recurrent pancreatic cancer is unclear. We aimed to evaluate the survival outcomes of pancreatic re-resection for locally recurrent pancreatic cancer following index pancreatectomy. A literature search was carried out in CENTRAL, EMBASE, MEDLINE, CINAHL, and Web of Science. Proportion meta-analysis model was constructed to quantify 1 to 5-year survival after pancreatic re-resection for locally recurrent pancreatic cancer. Random-effects modelling was applied to calculate pooled outcome data. Fifteen retrospective studies were included, reporting a total of 250 patients who underwent pancreatic re-resection for locally recurrent pancreatic cancer following their index pancreatectomy. Pancreatic re-resection was associated with 1-year survival 70.6% (95% confidence interval [CI], 65.0–76.2), 2-year survival 38.8% (95% CI, 28.6–49.0), 3-year survival 20.2% (95% CI, 13.8–26.7), and 5-year survival 9.2% (95% CI, 5.5–12.8). The between-study heterogeneity was insignificant in all outcome syntheses. Repeat pancreatectomy for local recurrence of pancreatic cancer in the remnant pancreas following the index pancreatectomy is associated with acceptable overall patient survival. We recommend selective re-resection of such recurrences in younger patients with favorable tumor size and location. Our findings may encourage more robust studies to be conducted in this context to provide stronger evidence.

**Key Words:** Pancreas cancer; Local recurrence; Re-resection; Survival

## INTRODUCTION

Pancreatic ductal adenocarcinoma is associated with disappointing prognosis, since the overall 5-year survival rate has been reported to range 5% to 8% [1,2]. Although only surgical

resection can potentially cure the disease, the overall survival remains poor, with a reported 5-year survival rate of 12% to 19% after a successful pancreatectomy [3,4]. Such poor prognosis is due to a high rate of cancer recurrence (approximately 80%), even though a complete surgical resection is achieved [5].

Management of pancreatic cancer recurrence has traditionally been limited to best supportive care, with palliative chemotherapy offered to patients who have adequate performance status [6]. Nevertheless, recent evidence indicates that recurrent pancreatic cancer displays diverse behavior according to recurrence timing and location [7]. This includes both local recurrence and distant metastasis. Local recurrence is limited to the remnant pancreas, peripancreatic soft tissue, or locoregional lymph nodes [8,9]. Distant metastasis involves metastasis to a distant organ, distant lymph nodes, and/or the peritoneal space [10]. More recently, an isolated recurrence pattern has been introduced as the first recurrence limited to the remnant pancreas, a single lobe of the lung, a single lobe of the liver, or

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a single organ, such as the stomach, ovary, adrenal gland, or abdominal wall [11].

The role of surgical resection in patients with recurrent pancreatic cancer is unclear. However, several studies have reported survival benefit of repeat pancreatectomy for selected patients with recurrence in the remnant pancreas after the index pancreatectomy [5,8,9,12-14]. There is no comprehensive synthesis of evidence in this context. Although a meta-analysis of six studies compared the mean patient survival of resection versus no resection of pancreatic cancer recurrence, its findings may be of doubtful merit, considering that the non-resected group did not meet the criteria for resection, indicating that their recurrent disease were more severe and advanced [15]. This consideration subjects the findings of such comparison to significant bias, due to confounding by indication.

The purpose of this study was to conduct a meta-analysis of the best available evidence to evaluate the survival outcomes of pancreatic re-resection for locally recurrent pancreatic cancer following the index pancreatectomy.

## MATERIALS AND METHODS

### Design and study selection

We outlined our methodology in a review protocol. The standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16] were respected in the methodology of this study.

### Types of studies

All studies investigating the survival outcomes of pancreatic re-resection for locally recurrent pancreatic cancer following the index pancreatectomy were considered.

### Types of participants

All male or female adult patients (age more than 18 years) who underwent any type of pancreatectomy for local cancer recurrence following their index pancreatectomy were considered. The index pancreatectomy was defined as any type of pancreatectomy, including open, laparoscopic, or robotic classical pancreaticoduodenectomy (PD), subtotal stomach-preserving PD, pylorus-preserving PD (PPPD), total pancreatectomy (TP), distal pancreatectomy (DP), and central pancreatectomy (CP), for malignant or premalignant pathologies of the pancreas.

### Intervention of interest

The intervention of interest was defined as pancreatectomy for the local recurrence of pancreatic cancer. Other interventions, including exploration, palliative bypass, and other type of organ resection with no need for pancreatic re-resection, were excluded.

## Outcomes

We reported 1 to 5-year survival as categorical outcome measures to report the proportion of patients who were alive at a specific point during follow-up.

## Literature search strategy

A strategy for literature search was formulated and run via MEDLINE, CENTRAL, CINAHL, EMBASE, and Web of Sciences (Appendix 1). Moreover, evaluation of the reference lists of the identified studies or reviews was carried out by two independent authors. The literature search was performed on 18th December 2023.

## Study selection

An independent evaluation of the identified articles was performed by two reviewers. When required, their full texts were accessed, and carefully investigated against our inclusion and exclusion criteria. Studies that were deemed eligible were selected for inclusion. Discrepancies during this stage were addressed via detailed discussion among the assessors. If such disagreements remained unresolved, an independent assessor was involved.

## Extraction and management of data

A spreadsheet for data extraction was developed, and the information about the included studies, and outcome measures, were collected from all eligible studies by two assessors. Disagreements during this stage were also addressed by consultation with an independent assessor.

## Evaluation of risk of bias

The risk of bias assessment of the eligible studies was con-

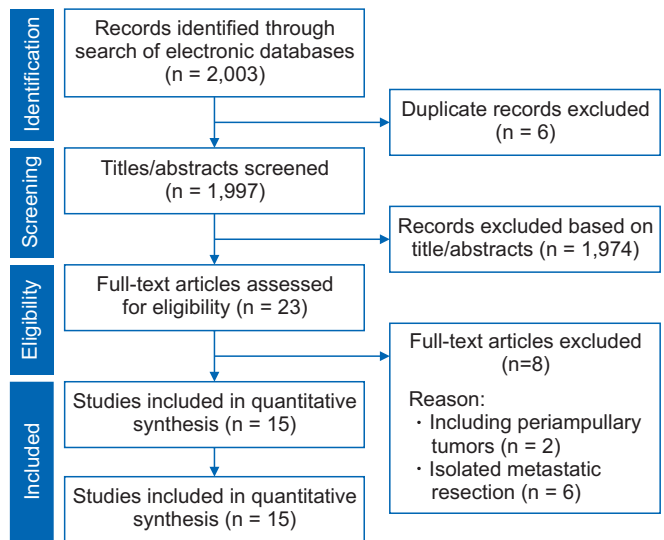


Fig. 1. PRISMA flow chart.

**Table 1.** Study-related data and baseline demographic and clinical characteristics of the included patients

Author	Year	Country	Journal	Sample size	Age (yr)	Sex	TNM stage	Index operation	Adjuvant CRT	Re-operation for local recurrence
Kleeff et al. [18]	2007	Germany	<i>Annals of Surgery</i>	10	NR	NR	II: 10	PD: 7 DP: 3	Yes: 4, No: 6	Not specified
Lavu et al. [19]	2011	USA	<i>Journal of Surgical Research</i>	11	69 (31–82)	6M/5F	NR	PD: 7 DP: 4	Yes: 8, No: 3	PD: 4 DP: 5 DP + adrenalectomy: 1 DP + subtotal gastrectomy: 1
Thomas et al. [8]	2012	USA	<i>Journal of Gastro-intestinal Surgery</i>	6	NR	NR	I or II: 6	NR	NR	NR
Strobel et al. [20]	2013	Germany	<i>Annals of Surgical Oncology</i>	41	NR	NR	NR	NR	NR	PD: 9 DP: 10, SPR: 5 Pancreatic resection + other organs: 14 Other: 3
Miyazak et al. [9]	2014	Japan	<i>Surgery</i>	11	67 (60–80)	6M/5F	I: 1 II: 8 III: 1 IV: 1	PD: 4 PD + PV: 2 PD + HR: 1 DP: 4	Yes: 6, No: 5	TP: 8 TP + PV: 1 TP + gastrectomy: 1 DP: 1
Hashimoto et al. [12]	2014	Japan	<i>Surgery Today</i>	8	70 (55–80)	4M/4F	I: 3 II: 5	PD: 4 DP: 4	Yes: 3, No: 5	TP: 6 TP + PV: 1 CP: 1
Shima et al. [13]	2015	Japan	<i>Langenbeck's Archives of Surgery</i>	6	66 (52–82)	3M/3F	I: 1 II: 5	PD: 3 PD + PV: 1 DP: 2	Yes: 1, No: 6	TP: 3 TP + PV: 2 DP: 1
Boone et al. [21]	2014	USA	<i>HPB</i>	7	NR	NR	II: 7	PD: 4 PD + PV: 1 DP: 2	NR	TP: 2 DP: 2 Resection of pancreatic bed mass: 1 Other: 2
Ishida et al. [22]	2016	Japan	<i>Pancreatology</i>	4	56 (50–62)	2M/2F	I: 2 II: 2	PD: 2 DP: 2	Yes: 4, No: 0	TP: 4
Chang et al. [23]	2016	Taiwan	<i>Medicine</i>	6	NR	NR	I: 6 II: 8	NR	NR	PD: 1 TP: 1 DP: 1 Other: 3
Suzuki et al. [5]	2016	Japan	<i>World Journal of Surgery</i>	12	59.5 (55–69)	6M/6F	I: 2 II: 9 IV: 1	PD: 3 PD + PV: 2 DPPHR: 1 DP: 6	Yes: 6, No: 6	TP: 8 TP + PV: 2 DP: 1 DPPHR: 1
Yamada et al. [24]	2018	Japan	<i>Surgery</i>	90	64.4 ± 8.3	50M/40F	0: 1 I: 26 II: 58 III: 4	PD: 53 DP: 36 CP: 1	Yes: 63, No: 27	PD: 37 DP: 53
Nakayama et al. [14]	2018	Japan	<i>Journal of Surgical Research</i>	11	68 (37–73)	8M/3F	I + II: 3 III + IV: 8	PD: 8 DP: 3	Yes: 10, No: 1	TP: 11
Kim et al. [11]	2019	South Korea	<i>British Journal of Surgery</i>	15	NR	NR	NR	NR	NR	TP or DP: 15
Lee et al. [25]	2021	South Korea	<i>Annals of Surgery Open</i>	12	NR	NR	NR	NR	NR	NR

TNM, tumor, node, metastasis; CRT, chemoradiotherapy; NR, not reported; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; SPR, segmental pancreatic resection; TP, total pancreatectomy; PV, portal vein resection; HR, hepatic resection; CP, central pancreatectomy; DPPHR, duodenum preserving pancreas head resection.

ducted by two authors using the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies [17]. The IHE checklist enables review authors to evaluate a single-arm series in the following aspects: study objective, study design, study population, intervention and co-intervention, outcome measure, statistical analysis, results and conclusions, and competing interests and sources of support. Disagreements following such assessment were addressed via discussion between the assessors. Where disagreements persisted, an additional author was involved.

**Data analysis**

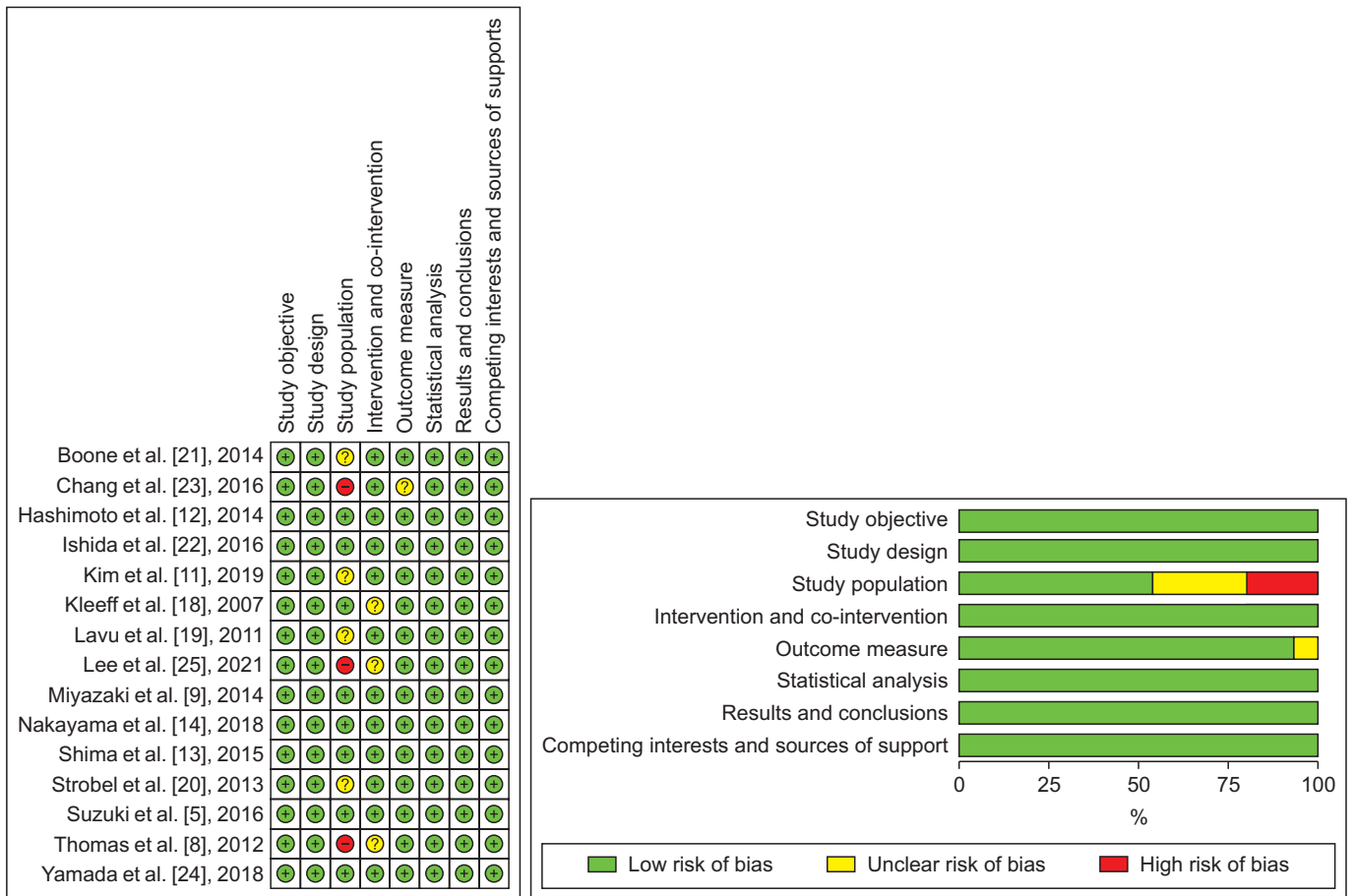
We used OpenMeta[Analyst] software (Brown School of Public Health) for analysis. The quantitative rates of 1 to 5-year survival were integrated from the included studies. This was followed by calculating an estimate of the overall effect. We used the DerSimonian–Laird random-effects method to determine the weighted summary proportions. Our analysis considered Intention to treat principles when dealing with the extracted data. An individual participant was considered as the unit of analysis. We evaluated heterogeneity through the cal-

ulation of  $I^2$  using the Cochran Q test ( $\chi^2$ ). Heterogeneity was subsequently interpreted whereby 0%–25% was mild, 26%–75% represented moderate heterogeneity, and 76%–100% represented considerable heterogeneity.

**RESULTS**

A total of 2,003 articles were detected following the literature search, of which 23 studies were short-listed for further assessment. An additional 8 articles were excluded, as 2 studies reported outcomes of all types of periampullary tumors, and 6 studies reported the outcomes of isolated pancreatic cancer recurrence anywhere, rather than just local recurrence. Finally, 15 retrospective studies [5,8,9,11-14,18-25] were considered eligible (Fig. 1). The included studies enrolled 250 patients who underwent pancreatectomy for locally recurrent pancreatic cancer following their index pancreatectomy.

Table 1 presents the first author, publication year, country of origin of the corresponding author, journal in which the study was published, sample size, type of index pancreatectomy performed, stage of resected pancreatic cancer, use of adjuvant



**Fig. 2.** Risk of bias summary and graph showing the authors' judgments about each risk of the bias item.

chemoradiotherapy, and type of re-pancreatectomy.

Of the included studies, 8 reported the median/mean age of the population of interest for this meta-analysis, which ranged 56 to 70 years. Considering the studies that reported the gender of their included patients, 56% of the patients were male, while the remaining 44% were female patients. The pathological staging of the primarily resected pancreatic cancer varied among the included studies, with stage II being the most common, followed by stage I, III, and a very few cases of stage IV disease. Ten studies reported the nature of the index pancreatectomies, which included 61.4% PD, 38.0% DP, and 0.6% CP. The adjuvant chemoradiotherapy was considered for 65.1% of the patients, while the remaining 34.9% did not receive any form of adjuvant treatment. Twelve studies provided information about the nature of pancreatic re-resections, which included 26.8% PD, 36.6% DP, 20.9% TP, 3.1% CP, and 12.6% unspecified.

### Evaluation of risk of bias

Fig. 2 outlines the results of risk of bias assessment of all included studies. The risk of bias associated with the study

population was low in 8 studies, unclear in 4 studies, and high in 3 studies. The risk of bias associated with intervention and co-intervention was low in 12 studies, and unclear in 3 studies. The risk of bias associated with outcome measure was low in 14 studies, but unclear in one study. The risk of bias associated with study objective, study design, statistical analysis, results, and conclusions, or competing interests and sources of support, were low in all the included studies.

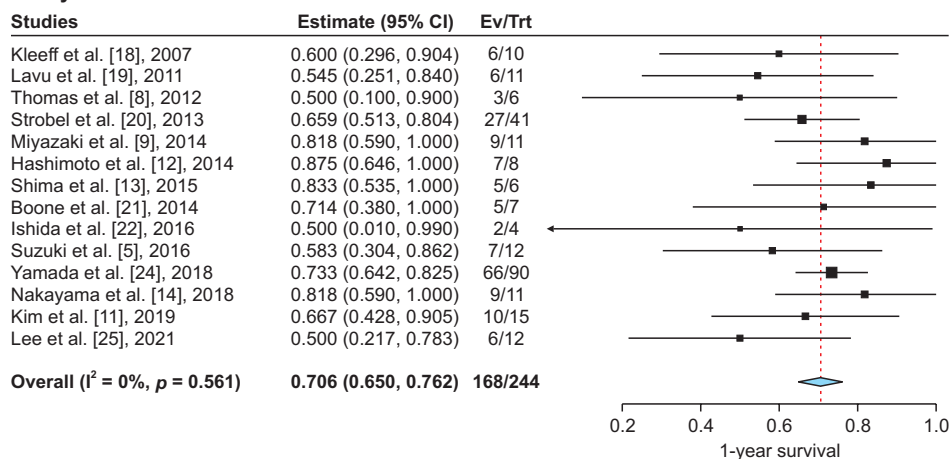
### Outcome data

Fig. 3 presents the results of the outcome syntheses.

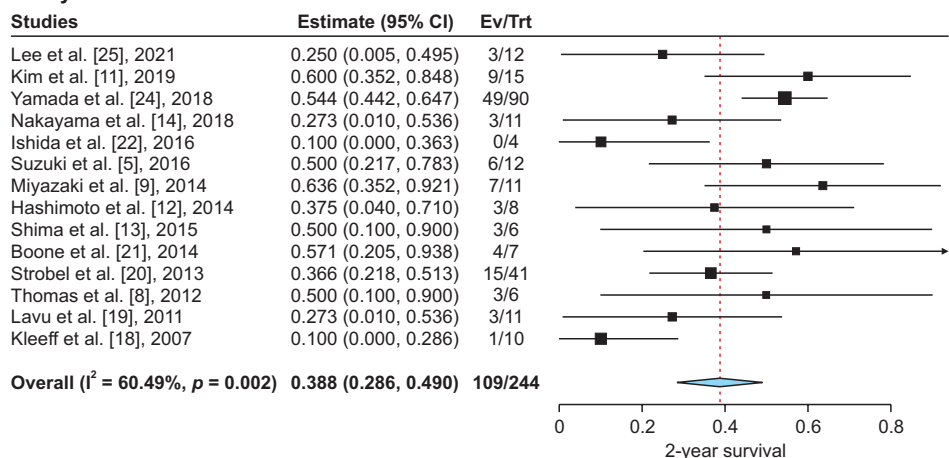
#### 1-year survival

Fourteen studies with a pooled population size of 244 patients were included in the analysis, which demonstrated that the 1-year survival rate after pancreatic re-resection was 70.6% (95% confidence interval [CI], 65.0–76.2) (Fig. 3A). A low level of heterogeneity was detected ( $I^2 = 0\%$ ,  $p = 0.561$ ).

#### A 1-year survival

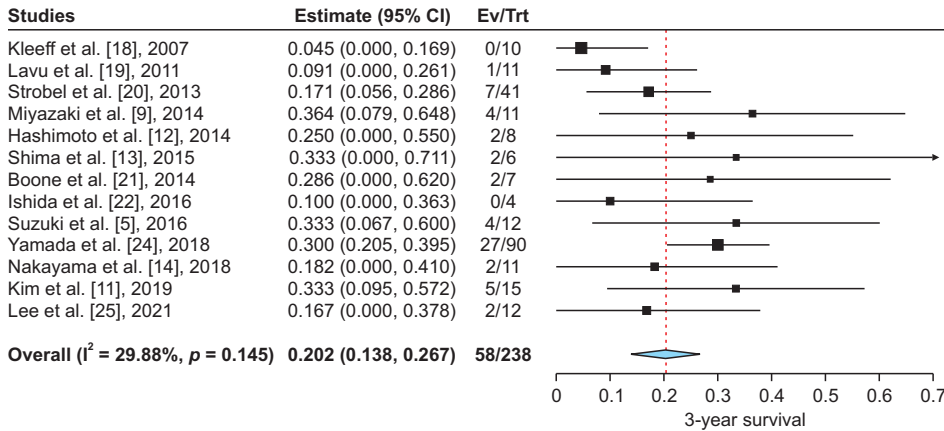


#### B 2-year survival



**Fig. 3.** Forest plots for proportion meta-analysis of the survival outcomes after re-resection of the local recurrence of pancreatic cancer: (A) 1-year survival, (B) 2-year survival, (C) 3-year survival, and (D) 5-year survival. CI, confidence interval; Ev/Trt, event/treatment.

**C 3-year survival**



**D 5-year survival**

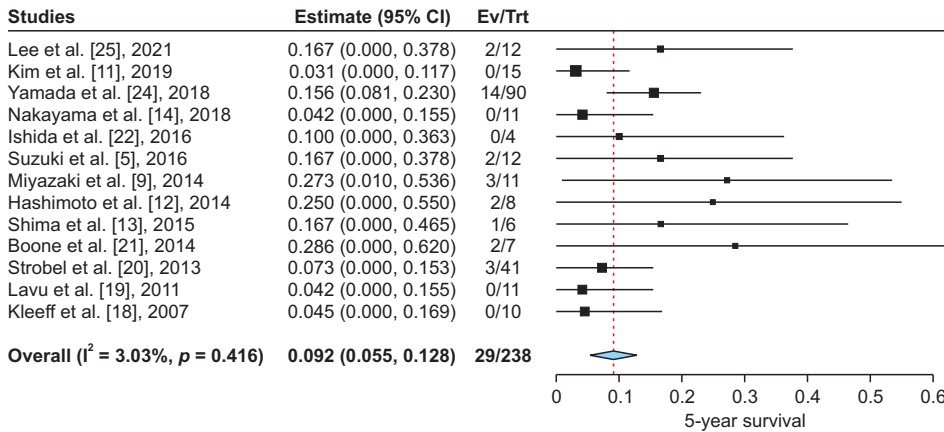


Fig. 3. Continued.

**2-year survival**

Fourteen studies with a pooled population size of 244 patients were included in the analysis, which demonstrated that the 2-year survival rate after pancreatic re-resection was 38.8% (95% CI, 28.6–49.0) (Fig. 3B). A moderate level of heterogeneity was detected ( $I^2 = 60.49\%$ ,  $p = 0.002$ ).

**3-year survival**

Thirteen studies with a pooled population size of 238 patients were included in the analysis, which demonstrated that the 3-year survival rate after pancreatic re-resection was 20.2% (95% CI, 13.8–26.7) (Fig. 3C). A moderate level of heterogeneity was detected ( $I^2 = 29.8\%$ ,  $p = 0.145$ ).

**5-year survival**

Thirteen studies with a pooled population size of 238 patients were included in the analysis, which demonstrated that the 5-year survival rate after pancreatic re-resection was 9.2% (95% CI, 5.5–12.8) (Fig. 3D). The between-study heterogeneity was low ( $I^2 = 3.03\%$ ,  $p = 0.416$ ).

**DISCUSSION**

There has been growing evidence in favor of repeat pancreatectomy for isolated recurrent pancreatic cancer in the remnant pancreas. A comprehensive systematic review and meta-analysis was conducted to evaluate the survival outcomes of pancreatic re-resection for locally recurrent pancreatic cancer following the index pancreatectomy. We identified 15 observational studies [5,8,9,11-14,18-25] reporting a total of 250 patients who underwent re-resection of the remnant pancreas for locally recurrent pancreatic cancer. The subsequent analyses demonstrated that pancreatic re-resection was associated with 1-year survival of 70.6%, 2-year survival of 38.8%, 3-year survival of 20.2%, and 5-year survival of 9.2%. The degree of heterogeneity among the analyzed studies was insignificant in the analysis of all evaluated outcomes.

Surgical resection of locally recurrent pancreatic cancer has been considered an attractive, albeit infrequent, approach to be included in a multimodal treatment strategy alongside other systemic treatments [26]. However, in the context of the management of isolated local pancreatic cancer recurrence, an established treatment strategy or a definitive guideline is lack-



ing. Similarly, no comprehensive evidence synthesis exists in the literature. Serafini et al. [15] conducted a meta-analysis of six studies to compare the outcomes of surgical resection and non-surgical treatments of recurrent pancreatic cancer, and reported that the overall survival and post-recurrence survival were significantly longer in the re-resected group. However, the patients in the non-resected group did not meet the criteria for any surgical resection, as their disease was too advanced, or had metastasis. For example, in both Hashimoto et al. [12] and Strobel et al. [20] (both included in the pooled analysis by Serafini et al. [15]), the patients who did not have resection were deemed to have unresectable disease, due to having distant metastasis or arterial involvement. Therefore, the findings of such comparison should be of doubtful merit due to the existence of significant bias, due to confounding by indication. It is important to highlight that a repeat pancreatectomy may be beneficial for a selected sub-group of patients who have a sufficient performance status and have recurrence limited to the remnant pancreas without any major vessel invasion, and with no active neural invasion, considering that in such cases, an R0 resection is relatively more likely to be achieved [27]. In fact, after a repeat pancreatectomy, the median survival seems to be relatively more favorable at 25–44 months in patients with recurrence limited to the pancreatic remnant [27]. Yamada et al. [24] identified the most favorable outcomes for re-resection in patients aged < 65 years with tumor size < 20 mm at least 10 mm away from the pancreatic stump. Whilst stratification of outcomes with respect to age, tumor size, or tumor distance from the pancreatic stump would have therefore been important, we were unable to do so, due to inconsistent reporting within the included studies.

The most performed type of index pancreatectomy in the included patients was PD (61.4%), followed by DP (38.0%). This may explain the relatively higher rate of distal/total remnant pancreatectomy (57.8%) as the most common type of repeat pancreatectomy procedure, when compared to PD (26.8%). Although our findings suggest acceptable survival rates of repeat pancreatectomy for local recurrence, it is worth highlighting that completion pancreatectomy is associated with endocrine and exocrine pancreatic insufficiency, with consequences that include diabetes and malabsorption. This also influences chemotherapy tolerance, whereby patients are more likely to suffer from diarrhea, hypoglycemia, and weight loss [22]. We were not able to evaluate such sequelae of repeat pancreatectomy in this meta-analysis. Furthermore, objective assessment of quality of life in such patient group deserves the attention of future research in this context.

Interestingly, most of the included studies were conducted in Asian countries, followed by the United States and Germany. To the best of our knowledge, there is no published case of repeat pancreatectomy for the local recurrence of pancreatic cancer in the United Kingdom (UK). Nevertheless, absence of evidence is not evidence of absence. Although, as a UK

based center, we had an experience in performing completion pancreatectomy for the local recurrence of pancreatic cancer following a PPPD with survival benefit for the treated patient, such experience was an isolated episode, which has never been translated into common practice. We believe there is a need for an established evidence-based guideline in this context. The findings of this meta-analysis can be utilized to design and conduct better quality studies to evaluate comparative outcomes of surgical resection versus non-surgical management of isolated locally recurrent pancreatic cancer in patients with comparable characteristics, to evaluate the real survival benefit of repeat pancreatectomy in such a patient group.

The available evidence is heterogenous about the use of chemotherapy before and after the re-resection of pancreatic cancer recurrence. Local recurrence of pancreatic cancer following the index pancreatectomy should be considered as an indication for systemic chemotherapy due to the high possibility of the presence of micrometastasis [28,29]. Whether or not the newly diagnosed cancer is a true local recurrence or a new primary lesion, neoadjuvant chemotherapy before re-resection may have some survival advantages. Adjuvant chemotherapy following pancreatic re-resection has also been demonstrated to significantly improve median survival in such patients' group [14]. However, the certainty and level of evidence remains low.

Readers of this study should consider its recognized limitations. The included studies had a retrospective nature, indicating that our results are at risk of bias associated with such study designs. This, together with the unclear or high risk of bias associated with the study population in nearly half of the included studies, can negatively impact the robustness of our findings. Although conducting a high-quality prospective comparative study in this context is challenging, the establishment of a best available evidence-based guideline in this context can subsequently encourage more frequent pancreatic re-resection for locally recurrent pancreatic cancer in selected patients, which can provide the opportunity to conduct higher quality studies with larger sample sizes in the future. The current meta-analysis is a single-arm meta-analysis, and does not provide any information about the potential advantages of repeat pancreatectomy over the non-surgical management of the local recurrence of pancreatic cancer in patients with homogenous disease characteristics. The sample sizes of the included studies were very small. We were unable to conduct our analyses with respect to the important determinants of outcomes, including tumor size, stage of the primary cancer, use of adjuvant chemotherapy after the index pancreatectomy, co-morbidities, or the type of index and repeat pancreatectomies.

#### Directions for future research

Considering our literature review and the findings of our meta-analysis, we encourage future studies:

- To consider the comparative outcomes of repeat pancre-

atectomy over the non-surgical management of the local recurrence of pancreatic cancer in patients with homogenous disease characteristics.

- To consider evaluation of the quality of life in patients undergoing pancreatic re-resection for locally recurrent pancreatic cancer.

## Conclusions

Repeat pancreatectomy for the local recurrence of pancreatic cancer in the remnant pancreas following the index pancreatectomy is associated with acceptable overall patient survival. The best available evidence is limited to small-sized retrospective single-arm studies, with the inherited risk of bias associated with their included populations. We recommend the selective re-resection of such recurrences in younger patients with favorable tumor size and location. Our findings may encourage more robust studies to be conducted in this context to provide stronger evidence.

## FUNDING

None.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: Shahin H, TSA. Data curation: Shahab H, DE. Methodology: Shahin H. Writing - original draft: Shahin H, Shahab H, DE. Writing - review & editing: All authors.

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**Appendix 1.** Search strategy

Search no.	Search strategy <sup>a)</sup>
#1	MeSH descriptor: [pancreatectomy] explode all trees
#2	pancreatectomy : TI,AB,KW
#3	MeSH descriptor: [pancreatic resection] explode all trees
#4	Pancreatic resection: TI,AB,KW
#5	#1 OR #2 OR #3 OR #4
#6	MeSH descriptor: [pancreatic cancer] explode all trees
#7	pancreatic cancer : TI,AB,KW
#8	MeSH descriptor: [recurrence] explode all trees
#9	recurrence: TI,AB,KW
#10	local : TI,AB,KW
#11	recurrent : TI,AB,KW
#12	locoregional: TI,AB,KW
#13	#6 OR #7 OR #8 OR #9 OR 10 OR #11OR#12
#14	#5 AND #13

<sup>a)</sup>This search strategy was adopted for following databases: MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL).