Improving outcomes of pancreatic surgery

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PART III

SURGICAL COMPLICATIONS IN PANCREATIC SURGERY

CHAPTER 9

Completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula after pancreatoduodenectomy: a multicentre cohort study and meta-analysis

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ABSTRACT

Background: Despite the fact that primary percutaneous catheter drainage has become standard practice, a few patients with pancreatic fistula after pancreatoduodenectomy ultimately undergo a relaparotomy. The aim of this study was to compare completion pancreatectomy to a pancreas-preserving procedure in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy.

Methods: This retrospective cohort study of nine institutions included patients who underwent relaparotomy for pancreatic fistula after pancreatoduodenectomy (2005-2018). Furthermore, a systematic review and meta-analysis was performed according to the PRISMA guidelines.

Results: From 4,877 patients undergoing pancreatoduodenectomy, 786 (16 per cent) developed a pancreatic fistula grade B/C and 162 (3 per cent) underwent a relaparotomy for pancreatic fistula. Of these patients, 36 (22 per cent) underwent a completion pancreatectomy and 126 (78 per cent) a pancreas-preserving procedure. Mortality was higher after completion pancreatectomy (20 (56 per cent) vs 40 patients (32 per cent); P=0.009), which remained after adjusting for sex, age, BMI, ASA score, previous reintervention, and organ failure in the 24h before relaparotomy (adjusted odds ratio 2.55, 95 per cent confidence interval 1.07-6.08). The proportion of additional reinterventions was not different between groups (23 (64 per cent) vs 84 patients (67 per cent); P=0.756). The meta-analysis including 33 studies evaluating 745 patients, confirmed the association between completion pancreatectomy and mortality (Mantel-Haenszel random-effects model: odds ratio 1.99, 95 per cent confidence interval 1.03-3.84).

Conclusions: Based on the current data, a pancreas-preserving procedure seems preferable to completion pancreatectomy in patients in whom a relaparotomy is deemed necessary for pancreatic fistula after pancreatoduodenectomy.

INTRODUCTION

Postoperative pancreatic fistula is among the most notorious complications after pancreatoduodenectomy as it is associated with a high morbidity and mortality.[1] Primary percutaneous catheter drainage has become standard practice in the management of a clinically relevant pancreatic fistula. However, percutaneous catheter drainage is not successful in all patients and a small subset ultimately undergo a relaparotomy.[2] An international survey showed good agreement between surgeons on the indication for relaparotomy when image-guided percutaneous catheter drainage of fluid collections is technically not feasible.[3]

During relaparotomy, different strategies are possible: surgical drainage (i.e. intra-abdominal lavage and placement of drains), repair or redo of the pancreatic anastomosis, salvage pancreatogastrostomy, and completion pancreatectomy.[4] Completion pancreatectomy is the most aggressive strategy which aims to completely remove the focus of intra-abdominal leakage and associated inflammation. Downsides of this procedure are the additional inflammatory stress by the extensive surgical procedure and subsequent possible deterioration of organ failure, technical difficulty resulting in blood loss, risk at damaging other structures and pancreatic exocrine and endocrine insufficiency. On the other hand, pancreas-preserving procedures might not be sufficient and thereby lead to further clinical deterioration including multiple organ failure, more reinterventions and prolonged hospital stay.[5, 6] Only few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy.[4]

The aim of this study was to evaluate surgical strategies (i.e. completion pancreatectomy vs pancreas-preserving procedure) in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy. Additionally, a systematic review and meta-analysis was performed to summarize the available evidence on this topic.

METHODS

Study design and patient selection

This was a retrospective multicentre cohort study of the Dutch Pancreatic Cancer Group[7] in which nine institutions participated. The need for informed consent was waived by the Medical Ethics Committee of the Leiden University Medical Centre. This study was reported according to the STROBE criteria.[8]

Included were all patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy from 2005 through 2018. The indication for relaparotomy was assessed by three independent authors (JVG, DK, JSDM) and discrepancies were resolved by consensus. Patients were identified using the prospective Dutch Pancreatic Cancer Audit (2013-2018). Participation in the Dutch Pancreatic Cancer Audit is mandatory for all institutions performing pancreatic surgery in the Netherlands.[9] In addition, an existing database[2] containing patients with severe pancreatic fistula after pancreatoduodenectomy (eight institutions, 2005-2013) was evaluated.

Data collection

Data were extracted from the Dutch Pancreatic Cancer Audit and through systematic evaluation of the medical records using a predefined case record form. Variables of interest included patient related variables: sex, age, Body Mass Index (BMI), pathology, preoperative biliary drainage, American Society of Anaesthesiologists (ASA)-score, surgery-related variables: type- and duration of surgery, pancreatic anastomosis, vascular resection, additional organ resection, blood loss, post-operative variables: postoperative complications, reinterventions, organ failure, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, systemic inflammatory response syndrome, duration of admission to the Intensive Care Unit (ICU), Clavien-Dindo classification, removal of abdominal drain, duration of hospital stay, postoperative mortality, follow-up variables: new onset postoperative exocrine insufficiency and diabetes mellitus and adjuvant therapy.

Definitions

Postoperative pancreatic fistula was defined and classified according to the International Study Group of Pancreatic Surgery criteria.[10] Mortality was defined as mortality during the index admission up to three months after discharge. Organ failure was defined as one or more of the following: respiratory organ failure (PaO_2 <60 mm Hg despite FiO_2 of 0.3 or need for mechanical ventilation), circulatory organ failure (systolic blood pressure <90 mm Hg despite adequate fluid resuscitation or need for inotropic support), or renal organ failure (creatinine level >2.0 mg/dL after rehydration or need for hemofiltration or haemodialysis). APACHE II score and SIRS criteria were scored 24h before and 24h after initial relaparotomy.[11, 12] SIRS was considered in case of ≥2 positive criteria.[12] Other pancreatic-specific complications (i.e. postpancreatectomy haemorrhage, bile leakage, delayed gastric emptying) were defined and classified according to the International Study Group of Pancreatic Surgery or Liver Surgery definitions.[13-15] Only grade B and C were reported as these are generally considered as clinically relevant. Duration of pancreatic fistula was calculated as time from pancreatoduodenectomy to removal of last abdominal catheter in patients undergoing a pancreas-preserving procedure. New onset postoperative exocrine pancreatic insufficiency and diabetes mellitus were defined as

need for oral pancreatic enzyme supplementation or antidiabetics within three months after discharge, not present before pancreatoduodenectomy. All data was collected which were available from the medical charts (from index admission up to three months after discharge).

Outcomes and comparison

The primary outcome was mortality (defined as mortality during the index admission up to three months after discharge). Secondary outcomes include organ failure and APACHE II score in 24h after initial relaparotomy, the number and type of additional reinterventions after initial relaparotomy, duration of Intensive Care Unit (ICU) stay, duration of hospital stay, new onset postoperative exocrine pancreatic insufficiency and diabetes mellitus, duration of pancreatic fistula in patients undergoing a pancreas-preserving procedure and proportion of patients with pancreatic cancer receiving adjuvant therapy.

Patient were divided into two groups based on the surgical strategy during the initial relaparotomy for pancreatic fistula: completion pancreatectomy vs pancreas-preserving procedure. A sensitivity analysis over time was performed stratified by period (2005-2008, 2009-2012, 2013-2015 and 2016-2018).

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). Continuous variables with a skewed distribution were presented as median (inter quartile range (IQR)) and compared by the Mann-Whitney U test. Categorical variables were presented as numbers (percentages) and compared by Chi-square or Fisher's Exact tests, as appropriate. Multivariable logistic regression analysis for mortality were conducted to adjust for theoretical confounding factors with sufficient available data (i.e. sex, age, BMI, ASA score, reintervention before initial relaparotomy and organ failure in the 24h before initial relaparotomy). Results are given as odds ratio (OR) with 95 per cent confidence interval (c.i.). All tests were two-sided and statistical significance was defined as $P<0.05$.

Systematic review and meta-analysis

A systematic literature search was performed according to the PRISMA guidelines.[16] The databases of PubMed, MEDLINE, Embase, Web of Science, and COCHRANE Library were searched for full-text, English-written studies. Titles, abstracts and full-text articles were screened by two independent authors (JVG, DK) for eligibility. Studies were included if patients were described who underwent relaparotomy for pancreatic fistula after pancreatoduodenectomy. Literature reviews and case reports were excluded. Data extraction was performed using a standardized form with study characteristics

and postoperative outcomes (i.e. mortality, duration of hospital stay, ICU admission, organ failure and additional reinterventions). The risk of bias was determined using the ROBINS-I tool for cohort studies.[17] A meta-analysis was performed for mortality (completion pancreatectomy vs pancreas-preserving procedure) using Review Manager (RevMan version 5.3). The I^2 statistic was used to assess heterogeneity between studies. An I^2 value of >50 per cent was considered as substantial heterogeneity. The Mantel-Haenszel random-effects model was used to calculate pooled effects. A fixed-effects models was used for sensitivity analysis.

RESULTS

Baseline characteristics

Of the 4,877 patients undergoing pancreatoduodenectomy, 786 (16 per cent) developed a pancreatic fistula grade B/C and 162 (3 per cent of all; 21 per cent of those with a pancreatic fistula) underwent a relaparotomy for pancreatic fistula (Figure 1). During initial relaparotomy for pancreatic fistula, completion pancreatectomy was performed in 36 (22 per cent) patients and a pancreas-preserving procedure in 126 (78 per cent) patients (Table 1). Strategies during an initial pancreas-preserving procedure included 80 patients (63 per cent) who had surgical drainage, 20 patients (16 per cent) with attempt to repair the pancreatic anastomosis, 21 patients (17 per cent) disconnection of the pancreatic anastomosis with preservation of the remnant and five patients (4 per cent) redo of the pancreatic anastomosis. Patients undergoing completion pancreatectomy were older (median 70 (66-73) vs 64 (58-71) years; P=0.025). In the completion pancreatectomy group, 13 patients (36 per cent) were ASA III-IV compared to 26 (21 per cent) patients in the pancreas-preserving group (P=0.055).

Patients undergoing completion pancreatectomy had more often single or multiple organ failure 24h before the initial relaparotomy (P=0.035). The highest APACHE II score within the 24h before the initial relaparotomy (median 14 (10-18) vs 12 (8-15); P=0.055), the proportion of reinterventions before the initial relaparotomy (17 patients (47 per cent) vs 57 patients (45 per cent); P=0.833) and the proportion of reinterventions for postpancreatectomy haemorrhage before the initial relaparotomy (6 patients (17 per cent) vs 12 patients (10 per cent); P=0.229) did not differ significantly between groups. The timing of initial relaparotomy also did not differ (median on postoperative day 10 (4-14) vs 9 (6-14); P=0.521). Other details regarding baseline characteristics, reinterventions and disease severity before initial relaparotomy are shown in Table S1.

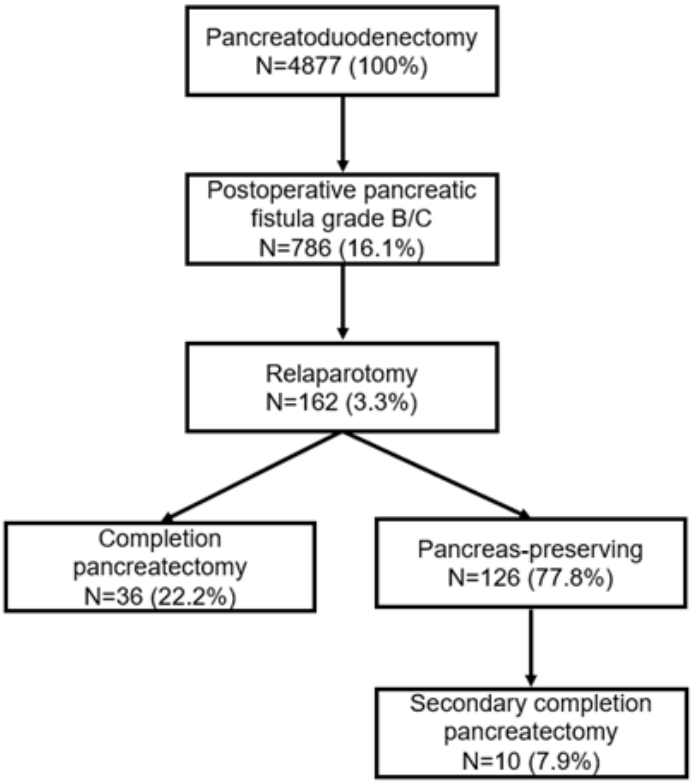

Figure 1. Flowchart of patient selection

Main outcomes

Main outcomes are summarized in Table 2. Patients undergoing completion pancreatectomy had a higher mortality rate, as compared to patients undergoing a pancreas-preserving procedure (20 patients (56 per cent) vs 40 patients (32 per cent); P=0.009). At multivariable analysis, adjusting for sex, age, BMI, ASA score, previous reintervention, and organ failure in the 24h before relaparotomy, completion pancreatectomy was associated with mortality (adjusted OR 2.55, 95 per cent c.i.1.07-6.08; Table 3).

There was no difference in the number of postoperative abdominal catheters after initial relaparotomy between groups (median 2 (1-2) vs 2 (2-3); P=0.119; 10 per cent missing data). Patients undergoing completion pancreatectomy had higher APACHE II scores within the 24h after initial relaparotomy (median 18 (15-23) vs 15 (11-18); P<0.001), whereas single or multiple organ failure (P=0.165) did not differ. The proportion of additional reintervention after initial relaparotomy was not different (23 patients (64 per cent) vs 84 patients (67 per cent); P=0.756). Out of 126 initial pancreas-preserving

Table 1. Baseline characteristics by surgical strategy for pancreatic fistula

		Strategy during initial relaparotomy for POPF				
		Completion pancreatectomy		Pancreas-preserving		
		N	%	N	%	P-value
Total		36	22.2	126	77.8	-
Baseline at time of index surgery						
Sex	**Female**	8	22.2	36	28.6	0.45
Age	**Median (IQR)**	70 (66 - 73)		64 (58 - 71)		0.025
BMI*	**Median (IQR)**	26.8 (24.2 - 28.9)		26.1 (23.4 - 28.7)		0.45
ASA	**III-IV**	13	36.1	26	20.6	0.06
Type of resection	**Whipple**	11	30.6	28	22.2	0.30
	PPPD	25	66.4	96	77.8	
Vascular resection		4	11.1	7	5.6	0.24
Additional organ resection		4	11.1	16	12.7	0.80
Pancreatic anastomosis	**Duct-to-mucosa PJ**	28	77.8	113	89.7	0.11
	Duct-to-mucosa PG	0		1	0.8	
	Dunking PJ	8	22.2	12	9.5	
Pathology	**Pancreatic cancer/ pancreatitis**	12	33.3	39	31.0	0.79
	Other	24	66.7	87	69.0	
Baseline at time of initial relaparotomy						
Previous reintervention		17	47.2	57	45.2	0.83
Radiological intervention		15	41.7	52	41.3	0.97
Relaparotomy		5	13.9	7	5.6	0.09
Previous reintervention for PPH		6	16.7	12	9.5	0.23
Radiological intervention for PPH		5	13.9	10	12.6	0.28
Relaparotomy for PPH		1	2.8	2	1.6	0.64
Organ failure 24h before*	**No**	19	52.8	68	54.8	0.035
	Single	6	16.7	39	31.5	
	Multiple	11	30.6	17	13.7	
Highest APACHE II score 24h before*	**Median (IQR)**	14 (10 - 18)		12 (8 - 15)		0.06
Postoperative day of initial relaparotomy for POPF	**Median (IQR)**	10 (4 - 14)		9 (6 - 14)		0.50

Abbreviations: POPF: postoperative pancreatic fistula; BMI: Body Mass Index; IQR: interquartile range; ASA: American Society of Anesthesiologists; PPPD: pylorus-preserving pancreatoduodenectomy ; PJ: pancreatojejunostomy; PG: pancreatogastrostomy; PPH: postpancreatectomy haemorrhage; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range; ICU: Intensive Care Unit

*Missing data: BMI (N=6), organ failure 24h before (N=2), highest APACHE II score 24h before (N=14),

procedures, 10 (8 per cent) patients ultimately underwent completion pancreatectomy. The proportion of additional reinterventions for postpancreatectomy haemorrhage after initial relaparotomy did not differ between groups (6 patients (17 per cent) vs 21 patients (17 per cent); P>0.999). In surviving patients, duration of hospital stay did not differ (median 55 (31-70) vs 56 (40-71) days; P=0.592). In surviving patients undergoing a pancreas-preserving procedure, 32 patients (43 per cent) developed new onset postoperative pancreatic exocrine insufficiency and 19 patients (26 per cent) developed new onset diabetes mellitus.

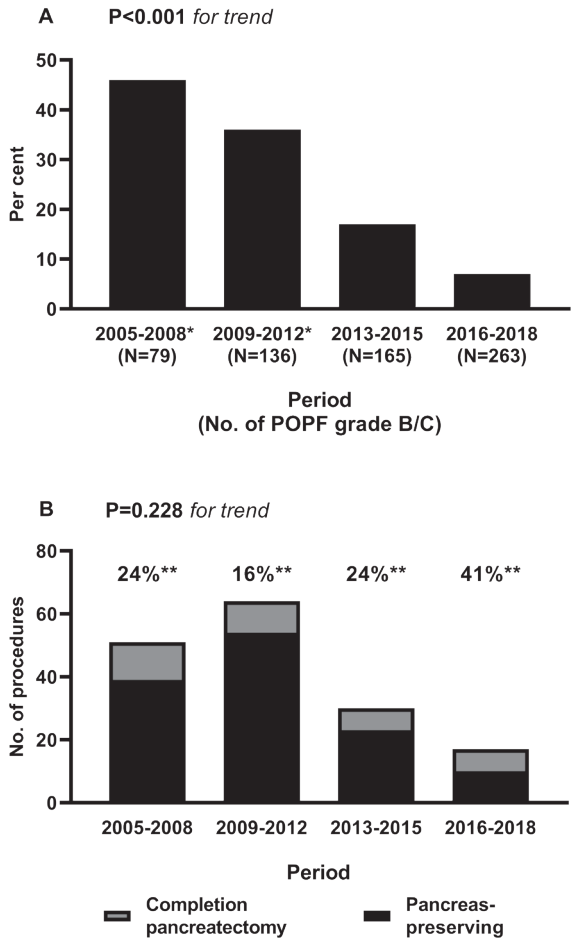

Figure 2. Sensitivity analysis for (A) proportion of patients undergoing relaparotomy for pancreatic fistula (B) and proportion of patients undergoing completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula. *Data from six of nine institutions; **numbers indicate the percentage of patients undergoing completion pancreatectomy

Table 2. Main outcomes by surgical strategy for pancreatic fistula

		Strategy during initial relaparotomy for POPF				
		Completion pancreatectomy		Pancreas-preserving		
		N	%	N	%	P-value
Total		36	22.2	126	77.8	
Mortality		20	55.6	40	31.7	0.009
Organ failure 24h after initial relaparotomy*	**No**	6	16.7	34	27.4	0.17
	Single	5	13.9	26	21.0	
	Multiple	25	69.4	64	51.6	
Highest APACHE II score 24h after initial relaparotomy*	**Median (IQR)**	18 (15 - 23)		15 (11 - 18)		<0.001
ICU admission		35	97.2	107	84.9	0.048
Duration ICU admission	**Median (IQR)**	13 (3 - 32)		7 (2 - 17)		0.09
Additional reintervention after initial relaparotomy		23	63.9	84	66.7	0.76
Radiological intervention		16	44.4	71	56.3	0.21
Relaparotomy		14	38.9	40	31.7	0.42
Secondary completion pancreatectomy		-		10	7.9	
Additional reintervention for PPH after initial relaparotomy		6	16.7	21	16.7	>0.99
Radiological intervention for PPH		2	5.6	12	9.5	0.46
Relaparotomy for PPH		4	11.1	10	7.9	0.55
Duration of hospital stay	**Median (IQR)**	38 (24 - 61)		53 (31 - 66)		0.07
Duration of hospital stay in survivors	**Median (IQR)**	55 (31 - 70)		56 (40 - 71)		0.59
New onset postoperative pancreatic exocrine insufficiency in survivors*		-		32	43.2	-
New onset postoperative diabetes mellitus in survivors*		-		19	25.7	-

Abbreviations: POPF: postoperative pancreatic fistula; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range; ICU: Intensive Care Unit; PPH: postpancreatectomy haemorrhage

*Missing data: organ failure 24h after (N=2), highest APACHE II score 24h after (N=28), new onset postoperative pancreatic exocrine insufficiency (N=14), new onset postoperative diabetes mellitus (N=14)

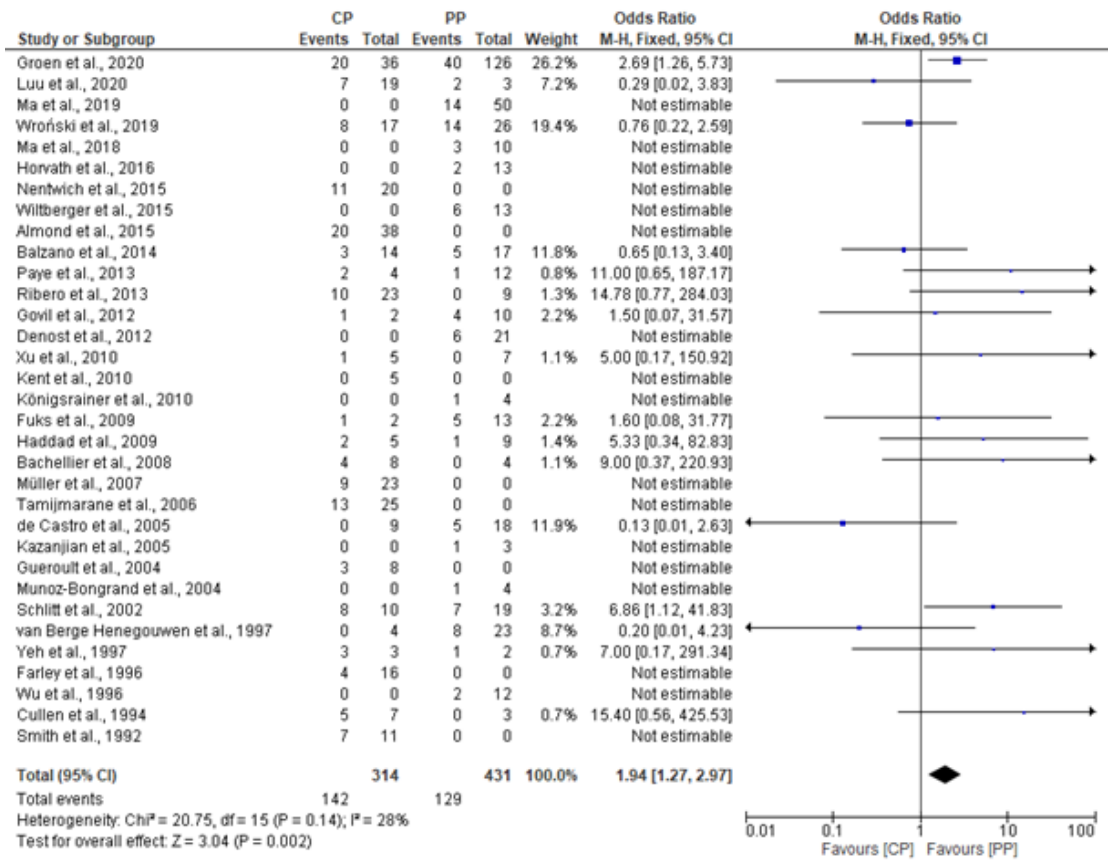

Figure 3. Forest plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) vs pancreas-preserving (PP) (random-effects model)

Other outcomes

Time to resolution of postoperative pancreatic fistula was 47 (25-69) days in patients undergoing a pancreas-preserving procedure (Table S2). One out of 5 (20 per cent) surviving pancreatic cancer patients who underwent a completion pancreatectomy received adjuvant therapy, as compared to one out of 25 patients (4 per cent) in the pancreas-preserving group (P=0.314). Other details regarding disease severity, reinterventions and other postoperative outcomes after initial relaparotomy are given in Table S2.

Sensitivity analysis by period

The sensitivity analysis stratified by period showed a linear decrease in proportion of patients undergoing relaparotomy for pancreatic fistula (P<0.001) and no linear change in proportion of patients undergoing completion pancreatectomy or a pancreas-preserving procedure (P=0.228) (Figure 2). The sensitivity analysis stratified by period also showed a higher mortality rate after completion pancreatectomy as compared to a pancreas-preserving procedure in all four periods (Table S3).

Table 3. Multivariable analysis for mortality

		Mortality		
		Odds ratio	**95% CI**	**P-value**
Strategy during initial relaparotomy	**Pancreas-preserving**	Reference		
	Completion pancreatectomy	2.55	1.07 - 6.08	0.035
Sex	**Male**	Reference		
	Female	1.97	0.87 - 4.44	0.10
Age		1.08	1.03 - 1.13	0.002
BMI*		1.02	0.93 - 1.12	0.70
ASA score	**I-II**	Reference		
	III-IV	0.89	0.38 - 2.07	0.79
Previous reintervention	**No**	Reference		
	Yes	1.12	0.56 - 2.38	0.71
Organ failure 24h before*	**No**	Reference		
	Single organ	1.15	0.49 - 2.69	0.76
	Multiple organ	2.47	0.91 - 6.68	0.08

Abbreviations: CI: confidence interval; BMI: Body Mass Index; ASA: American Society of Anesthesiologists

*Missing data: BMI or organ failure 24h before (N=7)

Systematic review and meta-analysis

The literature search identified 763 unique studies. After screening titles, abstracts and full-texts, 35 studies were included, which reported on patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy (Figure S1, Table S4). All included studies, except one, were retrospective of design and the number of included patients ranged 3-57. Five out of 35 studies were graded as moderate overall risk of bias, mainly due to confounding and lack of defining outcomes; the remaining studies did not provide sufficient information to determine the risk of bias in one or more domains of the ROBINS-I tool (Table S5). The meta-analysis consisted of 32 studies (583 patients) and the current study, with a total of 745 patients undergoing completion pancreatectomy or a pancreas-preserving procedure for pancreatic fistula. Mortality ranged from 0 to 100 per cent and completion pancreatectomy was associated with mortality (random-effects model, OR 1.99, 95 per cent c.i. 1.03-3.84, P=0.040; I^2=28 per cent; Figure 3). The funnel plot showed a symmetrical scatter around the mean (Figure S2). Sensitivity analysis showed a similar association between completion pancreatectomy and mortality (fixed-effects model, OR 1.94, 95 per cent c.i. 1.27–2.97; I^2=28 per cent; Figure S3).

Twenty-two surgical strategies during relaparotomy were described with varying definitions (Table S6). Overall. mean/median duration of hospital stay ranged from 15-62 days (23 studies and the current study), ICU admission after relaparotomy ranged from 38-100 per cent (5 studies and the current study), organ failure after relaparotomy ranged from 25-83 per cent (7 studies and the current study) and relaparotomy after relaparotomy ranged from 0-100 per cent (15 studies and the current study).

DISCUSSION

The current cohort study found that 1 in 5 patient with a postoperative pancreatic fistula grade B/C after pancreatoduodenectomy underwent a relaparotomy. Completion pancreatectomy was independently associated with a doubling of mortality, as compared to a pancreas-preserving procedure. The meta-analysis of 33 cohort studies confirmed this finding. Patients undergoing completion pancreatectomy had a higher APACHE II score within the 24h after relaparotomy, whereas there was no difference in the proportion of additional reinterventions or duration of hospital stay.

The rate of pancreatic fistula grade B/C in this study was fairly comparable to previous studies (16 vs 9-11 per cent)[1, 18], just as the rate of relaparotomy for pancreatic fistula (21 vs 17-37 per cent)[1, 18]. A recent study showed large variation in overall reoperation rate (6-17 per cent) between several pancreatic surgery registries in the United States of America and Europe.[19] The paradigm shift to percutaneous catheter drainage as primary

management of pancreatic fistula and advances in interventional radiology probably explain the linear decrease in proportion of patients undergoing relaparotomy over the study period. The systematic review of studies from 1992-2020 shows that a large variety of 22 surgical strategies during relaparotomy for pancreatic fistula are used or have been used in clinical practice. It remains unknown what the exact considerations are and it is likely that personal experience and preference influences the surgeon's choice. Completion pancreatectomy has been associated with a longer duration of surgery and more blood loss[5, 20], and a higher APACHE II score after relaparotomy in this study, which possibly illustrate that a completion pancreatectomy has a significant impact on the clinical condition of the patient. These factors should be considered when deciding to proceed with a completion pancreatectomy or a pancreas-preserving procedure.[21]

The high mortality after completion pancreatectomy may be explained by more severe tissue injury and inflammatory response in already critically ill patients. This effect was seen in a randomized trial in patients with necrotizing pancreatitis and secondary infection in which primary open necrosectomy was compared with a minimally invasive step-up approach[22] and in a matched cohort study in patients with pancreatic fistula in which relaparotomy was compared with catheter drainage as primary treatment.[2] Randomized trials on surgical strategies during relaparotomy for pancreatic fistula after pancreatoduodenectomy are currently not available. Such a trial would be difficult to perform as this population is increasingly rare, critically ill and it seems unlikely that surgeons will accept that the surgical strategy in this population is randomized.[23] Although the systematic review summarized the evidence on this topic, it should be noted that the included studies were all small, observational and heterogeneous. Despite the fact that the indications for relaparotomy may have varied and changed over time, mortality rates were higher after completion pancreatectomy in all four periods in the sensitivity analysis.

A theoretical advantage of completion pancreatectomy is that it removes the source of inflammation and thereby possibly decreasing the risk at additional reinterventions.[5, 20] The present and previous studies[2, 22] did not show less reinterventions after completion pancreatectomy. Furthermore, the risk of postpancreatectomy haemorrhage after the relaparotomy and required reinterventions (17 vs 17 per cent) was not different between the groups. Possibly, the actions applied by the surgeons were sufficient most of the times to prevent erosion of the peripancreatic vascular structures by leaking pancreatic enzymes.[24] A recent study showed that pancreatic fistula and postpancreatectomy haemorrhage can develop independently and have a major impact on organ failure and mortality.[25] The Dutch Pancreatic Cancer Group is currently analysing the data of the nationwide PORSCH trial to investigate whether early recognition and a minimally invasive step-up approach for pancreatic fistula after pancreatic resection decreases the

risk at postpancreatectomy haemorrhage, organ failure and mortality.[26] Of note, current study was not designed to promote relaparotomy over percutaneous catheter drainage as primary management of pancreatic fistula and the authors emphasize that a minimally invasive step-up approach should be the preferred strategy.

Little is known on new onset pancreatic exocrine insufficiency, one study reported a rate of 67 per cent (43 per cent in current study).[27] More studies reported on new onset diabetes mellitus, ranging 26-50 per cent (26 per cent in current study).[20, 27-30] A recent meta-analysis showed an acceptable rate of diabetes related morbidity and levels of HbA1c one year after elective or emergency, total pancreatectomy.[31] Unfortunately, these data were not available for the current study. In the previously mentioned meta-analysis, diarrhoea was the most frequent symptom (24 per cent), which may be caused by pancreatic exocrine insufficiency or autonomic denervation of the bowel due to the extent of the resection.[31] In the Netherlands, initiatives like the PACAP-1 trial are aimed to improve pancreatic enzyme replacement therapy in patients with pancreatic cancer.[32]

The results of the current study should be interpreted in light of some limitations. First, some data were retrospectively collected and this holds the risk of information and classification bias. The data extracted from the prospective Dutch Pancreatic Cancer Audit has been previously validated for data accuracy.[9] Second, due to the observational design of this study, confounding by indication is an important potential bias as the surgeon's decision to perform a completion pancreatectomy or pancreas-preserving procedure is based on the experience and personal preferences of the surgeon and the clinical and surgical context of the patient. For example, patients with completion pancreatectomy were older and had more often multiple organ failure. Inherent differences between patients undergoing a completion pancreatectomy compared to a pancreas-preserving procedure may partly explain the observed results. The multivariable analysis was limited by the sample size and could only adjust for a few possible confounders. Also, data of some other possible confounders, for example blood loss and the use of antibiotics[1], were not sufficiently available. Due to these limitations, residual confounding cannot be ruled out and results have to be interpreted with caution. Strengths of this study include the detailed data of disease severity and reinterventions before and after the initial relaparotomy and the systematic review of available evidence.

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SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics, reinterventions and disease severity before relaparotomy by surgical strategy for pancreatic fistula

		Strategy during initial relaparotomy for POPF				
		Completion pancreatectomy		Pancreas-preserving		
		N	%	N	%	P-value
Total		36	22.2	126	77.8	
Baseline at time of index surgery						
Biliary drainage		20	55.6	68	54.0	0.866
Duration of surgery (min)*	**Median (IQR)**	317 (249 - 440)		341 (259 - 429)		0.680
Blood loss (mL)*	**Median (IQR)**	1450 (850 - 2000)		636 (401 - 1200)		0.016
Postoperative abdominal catheter(s)		36	100.0	122	96.8	0.279
Reinterventions before initial relaparotomy						
N of radiological interventions	**Median (IQR)**	0 (0 - 1)		0 (0 - 1)		0.651
N of relaparotomies	**Median (IQR)**	0 (0 - 0)		0 (0 - 0)		0.147
Disease severity before initial relaparotomy						
ICU admission		18	50.0	52	41.3	0.351
Length of ICU admission	**Median (IQR)**	1 (0-4)		0 (0 - 2)		0.181
SIRS 24h before*		16	45.7	67	57.3	0.234
Respiratory organ failure 24h before		14	38.9	33	26.6	0.155
Circulatory organ failure 24h before		11	30.6	31	25.0	0.505
Renal organ failure 24h before		8	22.2	13	10.5	0.066
Details of initial relaparotomy						
Duration of surgery (min)*	**Median (IQR)**	128 (100 - 162)		93 (66 - 145)		0.028
Blood loss (mL)*	**Median (IQR)**	1400 (800 - 3500)		300 (50 - 1000)		0.025
Dehiscence anastomosis*	**Intact**	0		14	19.2	0.024
	Partial	28	87.5	54	74.0	
	Complete	4	12.5	5	6.8	

Table S1. Continued

Condition of the pancreatic remnant*	**Normal**	1	6.3	2	5.7	0.774
	Oedema	1	6.3	2	5.7	
	Inflammatory	4	25.0	14	40.0	
	Necrotic	10	62.5	17	48.6	

Abbreviations: POPF: postoperative pancreatic fistula; FRS: Fistula Risk Score; IQR: interquartile range; PPH: postpancreatectomy hemorrhage; SIRS: systemic inflammatory response syndrome; ICU: Intensive Care Unit
*Missing data: duration of surgery (N=6), blood loss (N=76), SIRS 24h before (N=10), respiratory organ failure 24 before (N=2), circulatory organ failure 24 before (N=2), renal organ failure 24 before (N=2), duration of surgery (N=80), blood loss (N=134), dehiscence anastomosis (N=67), condition of the pancreatic remnant (N=111)

Table S2. Disease severity, reinterventions and other postoperative outcomes after relaparotomy by surgical strategy for pancreatic fistula

		Strategy during initial relaparotomy for POPF				
		Completion pancreatectomy		Pancreas-preserving		
		N	%	N	%	P-value
Total		36	22.2	126	77.8	
Disease severity after initial relaparotomy						
SIRS 24h after*		17	50.0	47	43.9	0.535
Respiratory organ failure 24h after		28	77.8	78	62.9	0.097
Circulatory organ failure 24h after		23	63.9	71	57.3	0.477
Renal organ failure 24h after		17	47.2	30	24.2	0.008
Additional reinterventions after initial relaparotomy						
N of radiological interventions	**Median (IQR)**	0 (0 - 2)		1 (0 - 2)		0.152
N of relaparotomies	**Median (IQR)**	0 (0 - 1)		0 (0 - 1)		0.280
Reinterventions in total						
N of interventions	**Median (IQR)**	4 (2 - 5)		3 (2 - 5)		0.455
N of relaparotomies	**Median (IQR)**	1 (1 - 2)		1 (1 - 2)		0.153
Radiological intervention		23	63.9	90	71.4	0.849
N of radiological interventions	**Median (IQR)**	1 (0 - 3)		2 (0 - 3)		0.409
Postoperative course in total						
PPH		16	44.4	57	45.2	0.933
Bile leakage		11	30.6	37	29.4	0.890
Delayed gastric emptying		25	86.2	89	80.2	0.457
ICU admission		35	97.2	110	87.3	0.087
Duration of ICU stay	**Median (IQR)**	17 (5 - 35)		8 (3 - 18)		0.026
Duration of ICU stay in survivors	**Median (IQR)**	14 (5 - 35)		7 (3 - 16)		0.077
Clavien-Dindo	**IIIb**	2	5.6	26	20.6	0.020
	IVa	7	19.4	41	32.5	

Table S2. Continued

	IVb	8	22.2	21	16.7	
	V	19	52.8	38	30.2	
Duration of POPF in survivors	**Median (IQR)**	-		47 (25 - 69)		-
Adjuvant therapy in survivors with pancreatic cancer		1	20.0	1	4.0	0.314

Abbreviations: POPF: postoperative pancreatic fistula; SIRS: systemic inflammatory response syndrome; IQR: interquartile range; PPH: postpancreatectomy hemorrhage; ICU:Intensive Care Unit

*Missing data: SIRS 24h after (N=21), respiratory organ failure 24 before (N=2), circulatory organ failure 24 before (N=2), renal organ failure 24 before (N=2), delayed gastric emptying (N=22), duration of POPF in survivors (N=10)

Table S3. Sensitivity analysis for previous reintervention, organ failure and APACHE II score before initial relaparotomy and mortality by surgical strategy for pancreatic fistula stratified by period

			Treatment during initial relaparotomy for POPF				
			Completion pancreatectomy		Pancreas-preserving		
			N	%	N	%	P-value
	Total		36	22.2	126	77.8	
2005-2008	**Previous reintervention**		4	33.3	14	35.9	0.871
	Organ failure 24h before*	**No**	7	58.3	18	48.6	0.096
		Single	1	8.3	14	37.8	
		Multiple	4	33.3	5	13.5	
	Highest APACHE II score 24h before*	**Median (IQR)**	11 (7-16)		11 (7-15)		0.810
	Mortality		5	41.7	11	28.2	0.379
2009-2012	**Previous reintervention**		4	40.0	24	44.4	0.795
	Organ failure 24h before*	**No**	5	50.0	36	66.7	0.397
		Single	3	30.0	14	24.9	
		Multiple	2	20.0	4	7.4	
	Highest APACHE II score 24h before*	**Median (IQR)**	13 (10-18)		11 (8-14)		0.170
	Mortality		6	60.0	18	33.3	0.110
2012-2015	**Previous reintervention**		4	57.1	12	52.2	0.818
	Organ failure 24h before*	**No**	4	57.1	10	43.5	0.585
		Single	1	14.3	8	34.8	
		Multiple	2	28.6	5	21.7	
	Highest APACHE II score 24h before*	**Median (IQR)**	15 (11-21)		12 (11-16)		0.360
	Mortality		6	85.7	8	34.8	0.018
2016-2018	**Previous reintervention**		5	71.4	7	70.0	0.949
	Organ failure 24h before*	**No**	3	42.9	4	40.0	0.729
		Single	1	14.3	3	30.0	
		Multiple	3	42.9	3	30.0	
	Highest APACHE II score 24h before*	**Median (IQR)**	15 (14-17)		12 (9-16)		0.230
	Mortality		3	42.9	3	30.0	0.585

Abbreviations: POPF: postoperative pancreatic fistula; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range

*Missing data: organ failure 24h after (N=2), highest APACHE II score 24h after (N=28)

Table S4. Overview of studies on surgical strategy for pancreatic fistula

Author	Publishing year	Journal	Nation	Design	Time period	Inclusion criteria main study	No. patients with relaparotomy for POPF	Definition of fistula
Groen	2020	Current study	NL	Retrospective	2005-2018	Relaparotomy for POPF	162	ISGPS
Luu	2020	J Hepatobiliary Pancreat Sci	Germany	Retrospective	2007-2016	PD	23	ISGPS
Qiu	2019	J Cancec Res Ther	China	Retrospective	2010-2018	PD	5	-
Ma	2019	Int J Surg	China	Retrospective	2012-2016	Grade C POPF	53	ISGPS
Wroński	2019	HPB (Oxford)	Poland	Retrospective	2003-2017	Relaparotomy for POPF	43	ISGPS
Ma	2018	Int J Surg	China	Retrospective	2012-2016	Relaparotomy for POPF	11	ISGPS
Horvath	2016	Langenbecks Arch Surg	Germany	Retrospective	2004-2015	Relaparotomy for POPF	13	ISGPS
McMillan	2016	J Gastrointest Surg	USA	Retrospective	2003-2014	PD	57	ISGPS
Nentwich	2015	World J Surg	Germany	Retrospective	2002-2012	CP	20	ISGPS
Wiltberger	2015	J Surg Res	Germany	Retrospective	2005-2011	Relaparotomy for POPF	13	ISGPS
Almond	2015	HPB (Oxford)	UK	Retrospective	1987-2013	Elective and emergency CP	38	-
Balzano	2014	HPB (Oxford)	Italy	Retrospective	2004-2011	Relaparotomy for POPF	31	ISGPS
Addeo	2014	HPB (Oxford)	France	Retrospective	2004-2009	Relaparotomy for POPF	25	ISGPS
Paye	2013	Am J Surg	France	Retrospective	2005-2011	Relaparotomy for POPF	21	ISGPS
Ribero	2013	J Gastrointest Surg	Italy	Retrospective	1990-2010	Relaparotomy for POPF	42	ISGPS
Govil	2012	Indian Journal of Gastroenterology	India	Retrospective	1999-2011	Relaparotomy for POPF	36	ISGPS
Denost	2012	HPB (Oxford)	France	Retrospective	2004-2011	Relaparotomy for POPF	21	ISGPS
Xu	2010	World J Surg	China	Retrospective	1984-2005	Massive bleeding	12	-
Kent	2010	HPB (Oxford)	USA	Retrospective	2001-2009	Grade C POPF	5	ISGPS
Königsrainer	2010	Langenbecks Arch Surg	Germany	Retrospective	2004-2008	Relaparotomy for POPF	4	-

Table S4. Continued

Fuks	2009	Am J Surg	France	Retrospective	2000-2006	POPF	34	ISGPS
Haddad	2009	HPB (Oxford)	Brazil	Retrospective	2000-2006	POPF	14	Other
Bachellier	2008	Arch Surg	France	Retrospective	1988-2005	Relaparotomy for POPF	12	ISGPS
Müller	2007	Ann Surg	Germany	Prospective	2001-2006	TP	23	-
Tamijmarane	2006	Dig Surg	UK	Retrospective	1987-2005	CP	20	Other
de Castro	2005	Br J Surg	NL	Retrospective	1992-2002	PD	27	Other
Kazanjian	2005	Arch Surg	USA	Retrospective	1988-2004	PD	3	Other
Gueroult	2004	Arch Surg	France	Retrospective	1989-1999	CP for peritonitis	8	-
Munoz-Bongrand	2004	J Am Coll Surg	France	Retrospective	1990-2000	POPF	4	Other
Schlitt	2002	Br J Surg	Germany	Retrospective	1988-2000	PD	29	-
van Berge Henegouwen	1997	J Am Coll Surg	NL	Retrospective	1983-1995	PD	29	-
Yeh	1997	J Surg Res	Taiwan	Retrospective	1981-1992	PD with PJ	5	Other
Farley	1996	Br J Surg	Germany	Retrospective	1972-1994	CP	16	-
Wu	1996	Hepatogastroenterology	Taiwan	-	-	Relaparotomy for POPF	12	-
Cullen	1994	The American Journal of Surgery	USA	Retrospective	1980-1992	PD	10	Other
Smith	1992	World J Surg	USA	Retrospective	1964-1988	CP	11	-

Abbreviations: POPF: postoperative pancreatic fistula; ISGPS: International Study Group of Pancreatic Surgery; PD: pancreatoduodenectomy; CP: completion pancreatectomy; TP: total pancreatectomy; PJ: pancreatojejunostomy; NL: the Netherlands; USA: United States of America; UK: United Kingdom

Table S5. Risk of bias according the ROBINS-I tool

Author	Year	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Groen	2020	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Luu	2020	NI	Low	Low	Low	Low	Low	Low	NI
Qiu	2019	NI	Low	Low	Low	NI	NI	NI	NI
Ma	2019	NI	Low	Low	Low	Low	Low	Low	NI
Wroński	2019	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Ma	2018	NI	Low	Low	Low	Low	Low	Low	NI
Horvath	2016	NI	Low	Low	Low	Low	Low	Low	NI
McMillan	2016	NI	Low	Low	Low	NI	NI	NI	NI
Nentwich	2015	NI	Low	Low	Low	Low	Low	Low	NI
Wiltberger	2015	NI	Low	Low	Low	Low	Low	Low	NI
Almond	2015	NI	Low	Low	Low	Low	Low	Low	NI
Balzano	2014	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Addeo	2014	NI	Low	Low	Low	NI	NI	NI	NI
Paye	2013	NI	Low	Low	Low	Low	Low	Low	NI
Ribero	2013	NI	Low	Low	Low	Low	Low	Low	NI
Govil	2012	NI	Low	Low	Low	Low	Low	Low	NI
Denost	2012	NI	Low	Low	Low	Low	Low	Low	NI
Xu	2010	NI	Low	Low	Low	Low	Low	Low	NI
Kent	2010	NI	Low	Low	Low	Low	Moderate	Low	NI
Königsrainer	2010	NI	Low	Low	Low	Low	Low	Low	NI
Fuks	2009	NI	Low	Low	Low	Low	Low	Low	NI
Haddad	2009	NI	Low	Low	Low	Low	Low	Low	NI

Table S5. Continued

Bachellier	2008	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Müller	2007	NI	Low	Low	Low	Low	Low	Low	NI
Tamijmarane	2006	NI	Low	Low	Low	Low	Moderate	Low	NI
de Castro	2005	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Kazanjian	2005	NI	Low	Low	Low	NI	Low	Low	NI
Gueroult	2004	NI	Low	Low	Low	Low	Low	Low	NI
Munoz-Bongrand	2004	NI	Low	Low	Low	Low	Low	Low	NI
Schlitt	2002	NI	Low	Low	Low	Low	Low	Low	NI
van Berge Henegouwen	1997	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Yeh	1997	NI	Low	Low	Low	Low	Low	Low	NI
Farley	1996	NI	Low	Low	Low	Low	Low	Low	NI
Wu	1996	NI	Low	Low	Low	Low	Low	Low	NI
Cullen	1994	NI	Low	Low	Low	Low	Low	Low	NI
Smith	1992	NI	Low	Low	Low	Low	Low	Low	NI

Abbreviations: NI: not sufficient information

Table S6. Overview of reported outcomes of surgical strategies for pancreatic fistula

Author	Year	Groups	N	Mortality	Duration of hospital stay after relaparotomy, median (IQR)	ICU admission after relaparotomy	Organ failure after relaparotomy	Relaparotomy after relaparotomy
Groen	2020	CP	36	56%	38 (24 - 61)[a]	97%	83%	64%[a]
		PP	126	32%	39 (24 - 61)[a]	85%	73%	67%[a]
Luu	2020	CP	19	37%	-	-	-	-
		Reconstruction PJ	3	67%	-	-	-	-
		Suturing PJ	1	-	-	-	-	-
Qiu	2019	Simple drainage	5	-	-	-	-	-
Ma	2019	CP	2	-	-	-	-	-
		Surgical drainage	15	27%	38 (29 - 56)	-	-	14%
		EW	20	25%	20 (11 - 38)	-	-	5%
		Re-PJ	15	33%	35 (19 - 49)	-	-	14%
		PG	1	-	-	-	-	-
Wroński	2019	CP	17	47%	27 (3 - 32)	77%	63%[b]	24%
		Surgical drainage	16	56%	23 (11 - 36)	38%	25%[b]	56%
		EW	10	50%	25 (9 - 33)	80%	70%[b]	0%
Ma	2018	CP	1	-	-	-	-	-
		EW	10	30%	25 (9 - 41)	-	30%	-
Horvath	2016	EW	13	17%	58 (21 - 142)[f]	-	-	31%
McMillan	2016	CP	1	-	-	-	-	-
		Surgical drainage	26	-	-	-	-	-
		Revision PA	12	-	-	-	-	-
		Bridge stent	2	-	-	-	-	-
		Other	16	-	-	-	-	-

Table S6. Continued

Nentwich	2015	CP	20	55%	21 (1 - 113)[a]	-	-	70%
Wiltberger	2015	CP	3	-	-	-	-	-
		DAPR	13	46%	46 (33 - 96)[f]	100%[a]	-	16%
		Overstitching PJ	5	-	-	-	-	-
		Revision PJ	1	-	-	-	-	-
Almond	2015	CP	38	53%	27 (13 - 48)	-	-	-
Balzano	2014	CP	14	21%	22 (14)[c]	86%	-	7%
		Surgical drainage	10	30%	36 (24)[c]	50%	-	70%
		DO	7	29%	33 (25)[c]	43%	-	43%
Addeo	2014	CP	11	-	-	-	-	-
		Redo PJ	1	-	-	-	-	-
		PG	1	-	-	-	-	-
		Surgical drainage	15	-	-	-	-	-
Paye	2013	CP	4	50%	-	-	-	-
		Surgical drainage	5	-	-	-	-	-
		EW	12	8%	62 (29 - 156)[f]	-	33%	25%
Ribero	2013	CP	23	44%	27 (22 - 49)	-	-	39%
		ETP	9	0%	44 (24 - 52)	-	-	11%
Govil	2012	CP	2	50%	-	-	-	0%
		Surgical drainage	6	67%	-	-	-	67%
		Salvage PG	4	0%	-	-	-	0%
Denost	2012	CP	2	-	-	-	-	-
		EW	21	29%	42 (34 - 60)[f]	100%	67%	-

Table S6. Continued

Xu	2010	CP	5	20%	19 (7)[c]	-	-	-
		PJBA	7	0%	27 (7)[c]	-	-	-
Kent	2010	Bridge stent	5	0%	41 (8 - 77)	80%	80%	-
Königsrainer	2010	EW	4	25%	15 (11 - 17)[f]	-	-	50%
Fuks	2009	CP	2	50%	-	-	-	-
		DAPR	4	0%	-	-	-	-
		Surgical drainage	9	56%	-	-	-	-
Haddad	2009	CP	5	40%	52 (8 - 105)[g]	-	-	-
		Surgical drainage	9	11%	44 (14 - 95)[g]	-	-	-
Bachellier	2008	CP	8	50%	32[h]	-	50%	63%
		Salvage PG	4	0%	29[h]	-	0%	25%
Müller	2007	CP	23	39%	29 (8 - 43)	-	-	61%
Tamijmarane	2006	CP	25	52%	34 (8 - 105)[f]	-	32%	-
de Castro	2005	Surgical drainage	8	25%	31 (7 - 167)[i]	-	-	-
		DAPR	10	30%	43 (32 - 139)[i]	-	-	-
		CP	9	0%	44 (22 - 107)[i]	-	-	-
Kazanjian	2005	Revision PJ	3	33%	-	-	-	66%
Gueroult	2004	CP	8	38%	-	-	-	-
Munoz-Bongrand	2004	Surgical drainage	3	0%	49 (34 - 90)	-	-	66%[d]
		DAPR	1	100%	59	-	-	100%[d]
Schlitt	2002	CP	10	80%	-	-	-	-
		Suturing PA	8	31%[e]	-	-	-	-
		Re PA	8	31%[e]	-	-	-	-
		DAPR	3	66%	-	-	-	-

Table S6. Continued

van Berge Henegouwen	1997	CP	4	0%	55	-	-	-
		Surgical drainage	23	45%	74	-	-	-
Yeh	1997	CP	3	100%	-	-	-	-
		Surgical drainage	1	0%	-	-	-	-
		DAPR	1	100%	-	-	-	-
Farley	1996	CP	16	25%	24 (13 - 42)[f]	-	-	19%
Wu	1996	Oversewing PS	12	17%	-	-	-	-
Cullen	1994	CP	7	71%	-	-	-	-
		PP	3	0%	-	-	-	-
Smith	1992	CP	11	64%	46 (26 - 53)[f]	-	-	-

Abbreviations: CP: completion pancreatectomy; TP: total pancreatectomy; PP: pancreas-preserving; EW: external wirsungostomy; ETP: External Tube Pancreatostomy; DO: Duct Occlusion; PJ: pancreaticojejunstomy; PG: pancreatogastrostomy; PA: pancreatic anastomosis; PJBA: pancreaticojejunal bridge-anastomosis; disconnection of the anastomosis with preservation of the pancreatic remnant; PS: pancreatic stump

[a]In total
[b]On the day of relaparotomy
[c]Mean (standard deviation)
[d]Radiological intervention
[e]Taken together 5 out of 16 patients died
[f]Mean (range) in survivors
[g]Mean (range)
[h]Mean
[i]Median (range)

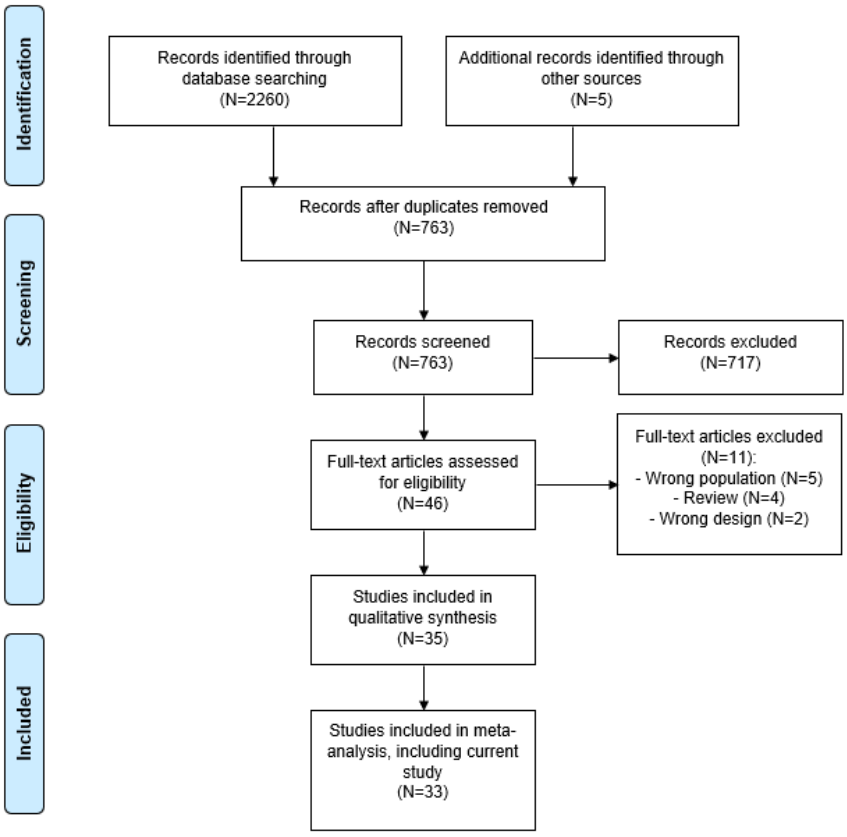

Figure S1. PRISMA flow diagram for the literature search

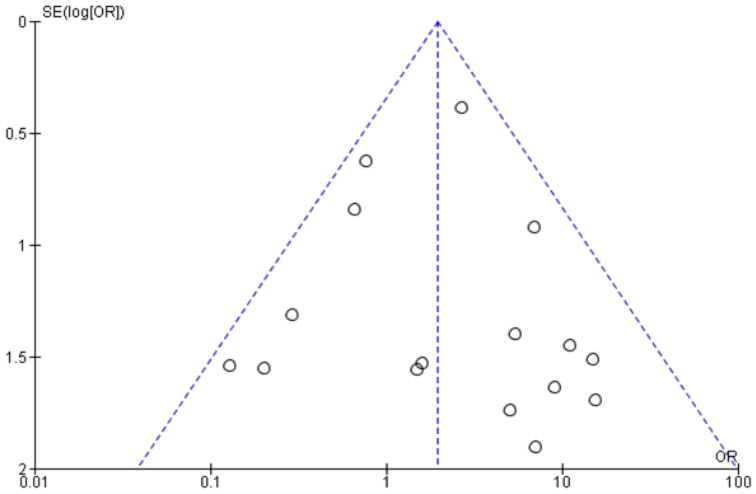

Figure S2. Funnel plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula

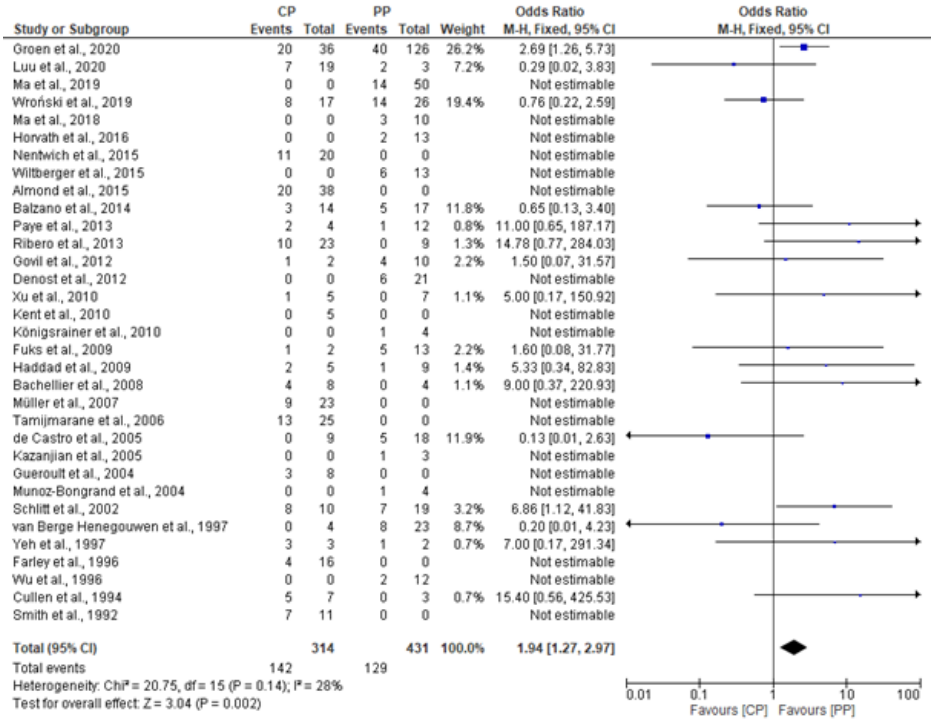

Figure S3. Forest plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) vs pancreas-preserving (PP) (fixed-effects model)