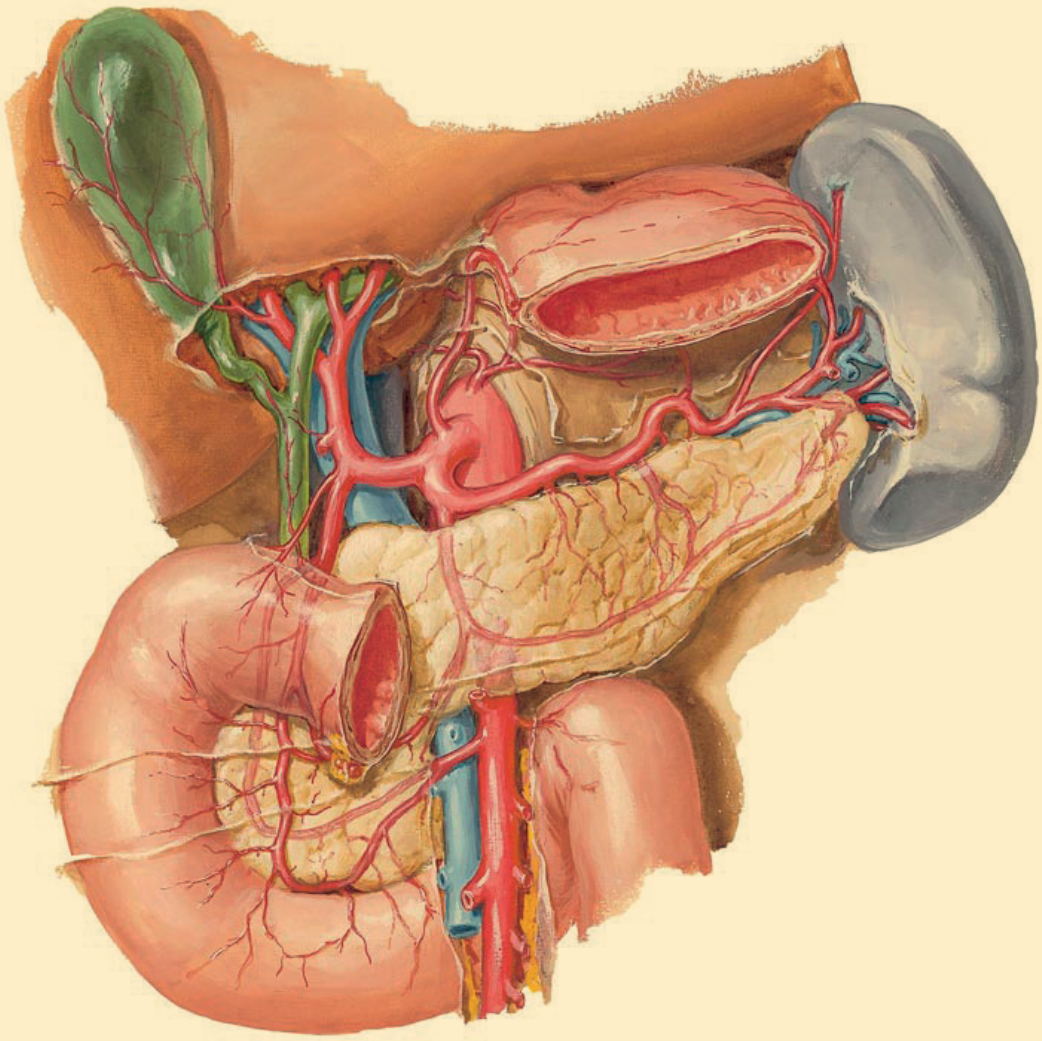
Improving outcomes of pancreatic surgery

Groen, J.V.

IMPROVING OUTCOMES OF PANCREATIC SURGERY



Jesse Vincent Groen

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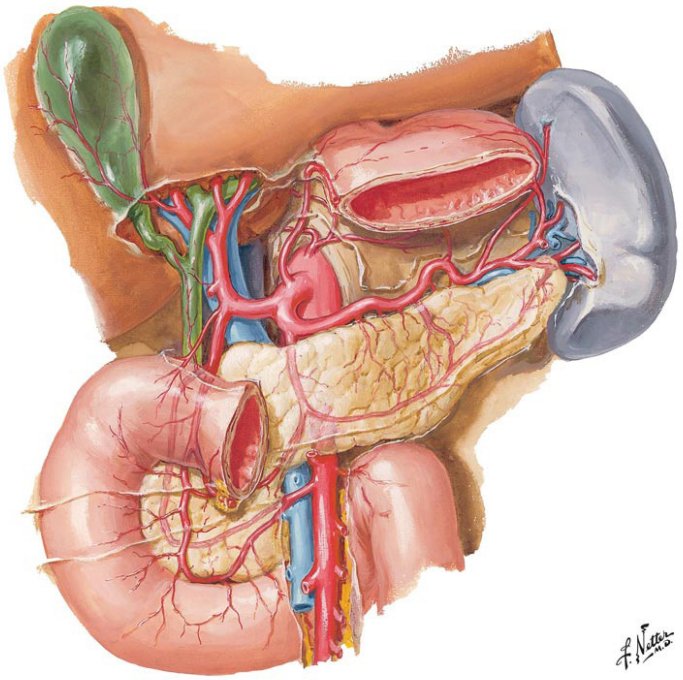

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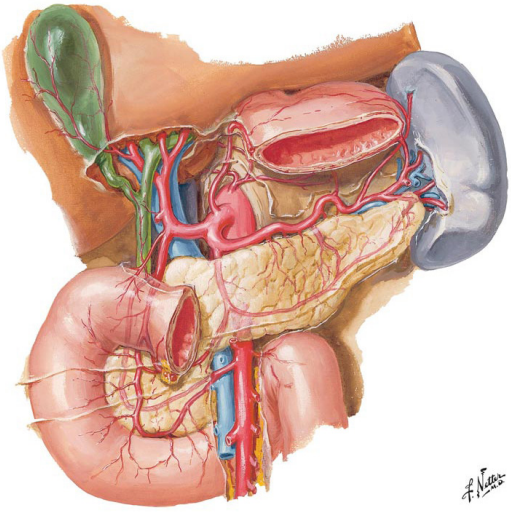
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

The pancreas

The pancreas is an abdominal organ located in the retroperitoneum, behind the stomach from just right of the aorta to the left where the spleen is located. The pancreas is ±15 centimeters long with a lobulated structure and a salmon-like color. The pancreas is divided in three parts: head, body, and tail. The pancreas has an endocrine (blood glucose levels) and exocrine function (digestive enzymes). Surgery on the pancreas is mostly performed for (pre)-malignant disease in the peri-ampullary region (pancreas, bile duct, duodenum, ampulla of Vater). The proximity to large vasculature (aorta, celiac trunk, superior mesenteric artery and vein, portal vein, inferior vena cave, renal artery and vein) and other organs (duodenum, stomach, gallbladder and ducts, liver, spleen, colon, kidneys, adrenal glands) makes surgery to the pancreas challenging. For this reason, the area is also called the "surgical soul" of the body. The pancreatoduodenectomy (Whipple procedure) is the most frequently performed procedure in which the pancreatic head, common bile duct, duodenum and sometimes the distal part of stomach are resected. During the reconstruction phase, the pancreas, duodenum or stomach and the common bile duct are anastomosed to the jejunum separately to restore gastrointestinal continuity.[1]

Pancreatic surgery is complex and technically demanding with historical high rates of postoperative morbidity and mortality. Over time, with advancement in surgical technique, perioperative management and dedicated high-volume institutions, the postoperative mortality has decreased from 20-30% in the early 1970s to approximately 2-3% in the last decade.[2, 3] In the Netherlands, the first initiatives to centralize pancreatic surgery were undertaken in 1997[4] and nowadays pancreatic surgery is only performed in institutions performing a minimum of 20 pancreatoduodenectomies annually.[5]



For pancreatic cancer, very little progress has been made in terms of long-term survival over the past decades.[6] Radical tumor resection combined with neoadjuvant or adjuvant chemo(radio)therapy is the current standard treatment.[7, 8] Resectability is mainly

determined by contact between the tumor and the venous and arterial vasculature.[9] Patients with stage I–II pancreatic cancer are generally considered eligible for resection. Unfortunately, about 80% of all patients are not eligible for resection due to advanced or metastatic disease at diagnosis.[10] Still, even after tumor resection of stage I–II pancreatic cancer, prognosis is poor, with a median overall survival of 17–30 months.[11]

Thesis outline

Pancreatic surgery today involves a wide variety of surgical and non-surgical medical disciplines. Multidisciplinary team meetings have been implemented in practice to increase the number of patients receiving optimal (oncological) diagnosis, treatment and follow-up and to decrease variations in treatment.[12] Enhanced recovery after surgery (ERAS) is a multidisciplinary guideline that has been introduced to decrease surgical stress and postoperative complications and increase recovery after surgery and the rate of patients receiving (oncological) adjuvant therapy. The general objective of this thesis is to improve the multidisciplinary management of pancreatic surgery and is divided in four parts.

Part I International evaluation of clinical practice in pancreatic surgery

Part I provides an overview of clinical practice regarding the variation in tumor resection and (neo)adjuvant therapy in patients with pancreatic cancer and an overview of the use of ERAS guidelines regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy.

The European Registration of Cancer Care (EURECCA) Pancreas Consortium uses cancer registry data to compare and improve treatment strategies by identifying best practices in a real-world scenario.[13] **Chapter 2** is the first study of the EURECCA Pancreas Consortium comparing (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (stage I and II) pancreatic adenocarcinoma in a national, regional and a single center cancer registry. A recent study with population-based data of multiple pancreatic cancer registries showed that the median age at diagnosis is 70 years.[14] This clearly differs from large randomized trials in pancreatic cancer in which the median age is 61–65 years.[15, 16] The aim of **Chapter 3** is to compare treatment strategies and survival outcomes of patients aged ≥70 years with stage I and II pancreatic cancer in the EURECCA Pancreas consortium.

There is increasing interest in ERAS guidelines as a means of improving clinical outcomes, although to date there is limited data on pancreatoduodenectomy.[17, 18] Pain management, fluid therapy and thromboprophylaxis are key elements in all ERAS

guidelines. **Chapter 4** aims to obtain an international assessment of current perioperative practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy among surgeons.

Part II Surgical and oncological aspects of venous resections in pancreatic surgery

Part II focusses on the surgical and oncological aspects of venous involvement (more specific the portal vein-superior mesenteric vein) in pancreatic surgery. Venous involvement will become increasingly important with the growing use of neoadjuvant therapy since it can increase the incidence of suspected venous involvement either by tumor fibrosis and inflammation, which can mimic venous tumor invasion on imaging, or by downstaging the tumor to resectable venous involvement.[19]

The aim of **Chapter 5** is to gain insights in the current surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement by international and Dutch surgeons and pathologists. Literature regarding risk of complications for the different types of venous resection is contradicting.[20-22] In **Chapter 6** we evaluate the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival in The Netherlands. To improve outcomes for patients with pancreatic cancer and venous involvement we need to identify best practices and standardize treatment in the Netherlands. **Chapter 7** explores the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands. One of the main challenges for a pancreatic surgeon when confronted with possible tumor invasion in the vein is distinguishing tumor from peritumoral inflammation and fibrosis. The aim of **Chapter 8** is to study the association between venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival.

Part III Surgical complications in pancreatic surgery

Part III consists of studies on the most notorious complications in pancreatic surgery: postoperative pancreatic fistula and abdominal infectious complications. These complications are associated with a high morbidity and mortality.

Only few studies have been performed on the clinical outcomes of different surgical strategies in patients with pancreatic fistula after pancreatoduodenectomy with a need for a relaparotomy.[23] **Chapter 9** evaluates surgical strategies (i.e. completion pancreatectomy versus pancreas-preserving procedure) in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy in nine Dutch institutions. Additionally, a systematic review and meta-analysis is performed on this topic to summarize all available evidence. In a recent study, Garnier et al. conclude that their standardized technique for completion pancreatectomy in patients with pancreatic

fistula after pancreatoduodenectomy appears to be relatively safe, reproducible, and could be particularly useful for young surgeons.[24] Additionally the authors state that pancreas-preserving surgical interventions are associated with more reoperations and mortality and that simple surgical drainage should not be adopted. **Chapter 10** contains a letter to the editor reacting to this study, we report a subgroup analysis of patients undergoing simple surgical drainage versus other pancreas-preserving surgical interventions.

When not caused by a pancreatic fistula, abdominal infectious complications are often caused by complications of the biliary or enteric anastomosis. No consensus exists about the predictive role of intraoperative bile cultures during pancreatoduodenectomy in abdominal infectious complications. A large multicenter study suggested that institution-specific internal reviews of intraoperative bile cultures should amend current protocols for antibiotic prophylaxis.[25] **Chapter 11** investigates the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy. Also, the predictive role of intraoperative bile cultures is evaluated by determining microorganism concordance in bile and cultures of abdominal infections. Additionally, a systematic review and meta-analysis summarizes all available evidence on this topic.

Part IV Perioperative anesthesiological management in pancreatic surgery

Part IV discusses the perioperative anesthesiological management in pancreatic surgery with special regards to analgesic and fluid therapy. Epidural analgesia is the perioperative analgesic technique of choice for most open abdominal surgical procedures and has been associated with better pain control.[26] On the other hand, it carries the risks of technique-specific complications, technical failure and hemodynamic instability. Therefore, the optimal analgesic technique after pancreatoduodenectomy remains under debate and detailed reports of perioperative analgesic management are lacking.

Chapter 12 describes a patient cohort treated with epidural analgesia versus non-epidural analgesia regarding the analgesic outcomes in the first ten postoperative days and clinical outcomes after open pancreatectomy in our own institution. In **Chapter 13** we assess whether epidural analgesia has superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy by a systematic review and meta-analysis of the literature. Recent studies and experience within our region have shown encouraging results and benefits of sublingual sufentanil (non-invasive, rapid absorption and pain relief, and less side effects) over epidural analgesia and iv morphine.[27] Therefore, we designed a randomized trial in patients undergoing pancreatoduodenectomy "*Postoperative Pain relief following Pancreatoduodenectomy (Triple P): sublingual sufentanil versus standard-of-care*". **Chapter 14** describes the results of this trial

in which sublingual sufentanil is compared to our standard-of-care (epidural analgesia or iv morphine). Finally, **Chapter 15** includes a general summary and discussion of the previous chapters, and discusses the future perspectives of pancreatic surgery and conclusions of this thesis.

Table 1. Research questions

Chapter 1	General introduction and outline of this thesis
PART I	**INTERNATIONAL EVALUATION OF CLINICAL PRACTICE IN PANCREATIC SURGERY**
Chapter 2	Is there variation in the use of (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (TNM stage I and II) pancreatic adenocarcinoma in the EURECCA Pancreas Consortium?
Chapter 3	How are treatment strategies and survival outcomes of patients aged ≥70 years with stage I–II pancreatic cancer in a real-world scenario in the Belgian, Dutch, and Norwegian national cancer registries?
Chapter 4	Is there international variation regarding pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy between pancreatic surgeons?
PART II	**SURGICAL AND ONCOLOGICAL ASPECTS OF VENOUS RESECTIONS IN PANCREATIC SURGERY**
Chapter 5	Is there variation regarding surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement between international experts and Dutch surgeons and pathologists?
Chapter 6	What is the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival?
Chapter 7	What are the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in in the Netherlands?
Chapter 8	Are venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival associated?
PART III	**SURGICAL COMPLICATIONS IN PANCREATIC SURGERY IN PANCREATIC SURGERY**
Chapter 9	What should be the preferred surgical strategy when performing a relaparotomy for pancreatic fistula after pancreatoduodenectomy?
Chapter 10	Correspondence to Garnier et al. and their study on standardized technique for completion pancreatectomy in patients with pancreatic fistula after pancreatoduodenectomy
Chapter 11	Do bile cultures obtained during pancreatoduodenectomy have added value in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy?
PART IV	**PERIOPERATIVE ANESTHESIOLOGICAL MANAGEMENT IN PANCREATIC SURGERY**
Chapter 12	What are the analgesic and clinical outcomes after epidural and non-epidural analgesia after open pancreatectomy?
Chapter 13	Does epidural analgesia have superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy in current the literature?
Chapter 14	Is sublingual sufentanil a non-inferior analgesic compared to standard-of-care in the treatment of postoperative pain in patients following pancreatoduodenectomy?
Chapter 15	General summary, discussion, future perspectives and conclusions

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PART I

INTERNATIONAL EVALUATION OF CLINICAL PRACTICE IN PANCREATIC SURGERY

CHAPTER 2

Differences in treatment and outcome of pancreatic adenocarcinoma stage I & II in the EURECCA Pancreas consortium

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ABSTRACT

Background: The EUropean REgistration of Cancer CAre (EURECCA) consortium aims to investigate differences in treatment and to improve cancer care through Europe. The aim of this study was to compare neo –and adjuvant chemotherapy (ACT) and outcome after tumor resection for pancreatic adenocarcinoma stage I & II in the EURECCA Pancreas consortium.

Methods: The eight collaborating national, regional and single center partners shared their anonymized dataset. Patients diagnosed in 2012-2013 who underwent tumor resection for pancreatic adenocarcinoma stage I & II were investigated with respect to treatment and survival and compared using uni- and multivariable logistic -and Cox regression analyses. All comparisons were performed separately per registry type: national, regional- and single center registries.

Results: In total, 2052 patients were included. Stage II was present in the majority of patients. The use of neo-ACT was limited in most registries (range: 2.8%-15.5%) and only different between Belgium and the Netherlands after adjustment for potential confounders. The use of ACT was different between the registries (range: 40.5%-70.0%), even after adjustment for potential confounders. Ninety-day mortality was also different between the registries (range: 0.9%-13.6%). In multivariable analyses for overall survival, differences were observed between the national –and regional registries, furthermore patients in ascending age groups and patients stage II showed a significant worse overall survival.

Conclusions: This study provides a clear insight in clinical practice in the EURECCA Pancreas consortium. The differences observed in (neo-)ACT and outcome give us the chance to further investigate the *best practices* and improve outcome of pancreatic adenocarcinoma.

INTRODUCTION

Pancreatic cancer (PC) is one of the few types of cancer with increasing incidence and mortality rates.[1] In 2017, the number of annual deaths in the European Union due to PC will exceed the number of death due to breast cancer.[2] Resection is the only chance for prolonged survival, unfortunately only 15-20% of PC patients are eligible for resection due to advanced -or metastatic disease at diagnosis.[3] Tumor/node/metastases (TNM) stage I & II PC are generally considered eligible for resection.[4] The European Society of Medical Oncology (ESMO) guidelines, during the study period and most recent, state that patients with a borderline resectable or locally advanced tumor should be treated with neoadjuvant chemotherapy (neo-ACT) in clinical trials whenever possible and that adjuvant chemotherapy (ACT) is considered as standard of care after curative resection for PC.[5,6] Recently, the ESPAC-4 trial showed a survival benefit in patients treated with adjuvant gemcitabine and capecitabine compared to gemcitabine alone.[7] Despite advances in (neo)-ACT, the median survival for patients with an initial resectable tumor is only 23.3 (range: 12-54) months.[8]

Previous studies have reported variations in incidence, mortality and survival in PC between countries.[9-12] The EUropean REgistration of Cancer CAre (EURECCA) consortium, established by the European CanCer Organisation (ECCO), aims to investigate differences in treatment and to improve cancer care through Europe.[13] International comparisons of (neo–)ACT and outcome in surgically treated patients with PC are sparse. Therefore, the aim of this study was to describe and compare (neo–)ACT and outcome of patients who underwent tumor resection for resectable (TNM stage I & II) pancreatic adenocarcinoma in the EURECCA Pancreas consortium.

MATERIALS AND METHODS

Study design & data preparation

This is an observational cohort study of eight partners (registries) in the EURECCA Pancreas consortium (national: Belgium (BE), the Netherlands (NL), Slovenia (SLO), Ukraine (UA) and Bulgaria (BG); regional: Catalonia (Spain) (CAT(E)) and Munich (Germany) (MU(D); and single center: Milan (Italy) (MIL(I))) who shared their anonymized dataset. Detailed description of the registries is provided in Table S1 (Supplementary). The American Joint Committee on Cancer and International Union Against Cancer TNM 7th Edition classification were used to describe stage.[4,14] In case pathology TNM variables were not informative (missing or X), clinical TNM variables were used as replacement. In case clinical TNM variables were also not informative (missing or X), pathology TNM variables were considered to be '0'. The 3rd edition of the International Classification of

Disease for Oncology was used for topographical- and morphological (i.e. pathologic diagnosis) coding.[15] Age was categorized as <65 years, 65-75 years and >75 years. Overall survival (OS) was calculated from date of surgery until date of death (event) or last follow-up (censored). Ninety-day mortality was calculated to distinguish surgery-related from disease-related death.[16]

Patient selection

All patients with pancreatic tumors (included codes: C25.0-C25.9; excluded: C25.4),[15] diagnosed in 2012-2013 (present in all registries), undergoing tumor resection, for adenocarcinoma (included codes: 8140-8380, 8500-8585; excluded: 8150-8158, 8240-8249), [15] stage I & II were included. Patients with a history of other malignancies were not excluded, since PC is most often determinative for the prognosis. BG could not confirm tumor resection and was only used in descriptive statistics in Table S2 (Supplementary). SLO and UA were not included in analyses of neo-ACT since no information was available. CAT(E) and UA were not included in analyses of ACT since no information was available.

Statistical analyses

Statistical analyses were performed using SPSS Inc. for Windows (version 23.0). Numerical data are reported as mean (standard deviation (SD)) and compared using the one-way ANOVA test. Categorical data are reported as absolute numbers (percentages) and compared using the Chi-square test. Multivariable logistics regression analyses (adjusted for sex, age group and stage) where performed for neo-ACT, ACT and 90-day mortality. Kaplan-Meier curves, Log-Rank tests and multivariable Cox regression analyses (adjusted for sex, age group, stage) where used to compare OS. For multivariable comparisons between registries, BE (national) and CAT(E) (regional) were used as reference groups (first in alphabetic order). For reasons of bias, comparisons were performed separately per registry type: national, regional- and single center registries. To assess the risk of missing data bias, sensitivity analyses were conducted by adding patients with 'unknown' stage to the original analyses. To assess the influence of 90-day mortality on the use of ACT, multivariable sensitivity analysis were performed with 90-day mortality as covariate. To assess the influence of use of (neo-)ACT on OS, multivariable sensitivity analysis were performed with (neo-)ACT as covariates. The original results were considered robust if the sensitivity analyses showed similar results. A P <0.05 was considered statistically significant for all analyses.

RESULTS

Patient & tumor characteristics

Figure S1 (Supplementary) illustrates the inclusion of patients in this study. In total, 2052 patients diagnosed in 2012-2013 underwent tumor resection for pancreatic adenocarcinoma stage I & II were included (Table 1). Distribution of males/females was largely comparable between the registries. The mean (SD) age differed between the national registries, ranging from 57.5 (11.8) years in UA to 66.7 (10.0) years in BE, and the regional registries, 67.4 (9.6) years in CAT(E) and 69.3 (9.2) years in MU(D). In all registries, stage II patients were the majority of patients undergoing tumor resection, ranging from 78.5% (UA) to 98.2% (MIL(I)). Overall, tumors were most often (73.6%) located in 'head of pancreas' and 'pancreaticoduodectomy' was performed in majority (81.2%) of patients, excluding SLO who did not specify type of resection. Table S2 (Supplementary) shows characteristics of patients for BG, who could not confirm tumor resection.

Neoadjuvant chemotherapy

Overall, the use of neo-ACT ranged from 2.8% in NL - 15.5% in MIL(I). There were no differences between the national and regional registries (Figure 1a-b).

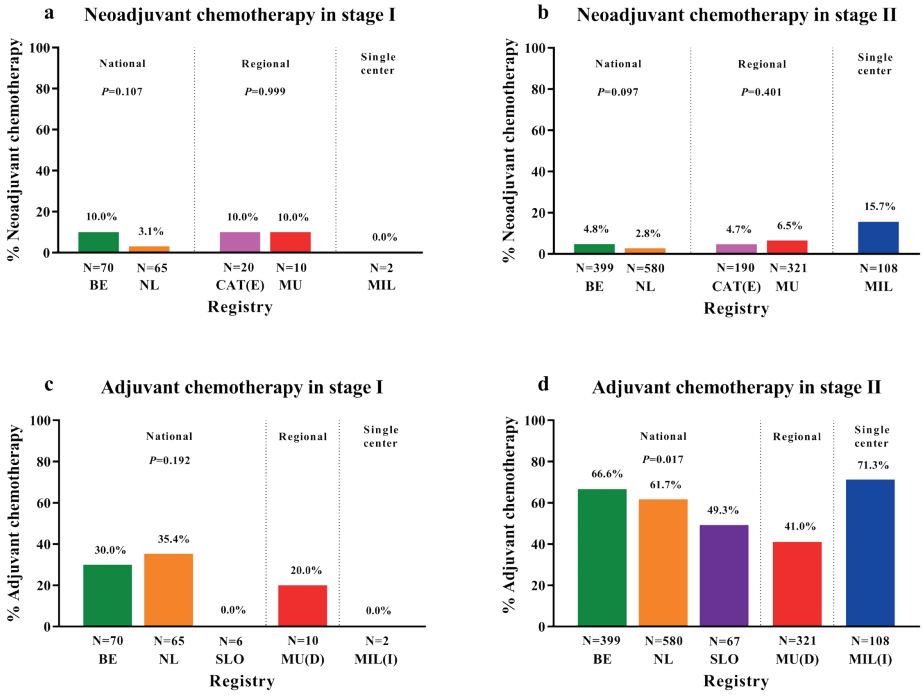

Figure 1a-d. Neo- and adjuvant chemotherapy per registry in (a) neoadjuvant chemotherapy in stage I, (b) neoadjuvant chemotherapy in stage II, (c) adjuvant chemotherapy in stage I, (d) adjuvant chemotherapy in stage II.

Table 1. Patient & tumor characteristics.

		Registry														
		National									Regional					Single center
		Belgium (*N*=469)		**The Netherlands (*N*=645)**		**Slovenia (*N*=73)**		**Ukraine (*N*=214)**			**Catalonia (*N*=210)**		**Munich (*N*=331)**			**Milan (*N*=110)**	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**	**p-value**	***N***	**%**	***N***	**%**	**p-value**	***N***	**%**
Sex	Male	256	54.6%	329	51.0%	39	53.4%	130	60.7%	0.098	116	55.2%	161	48.6%	0.135	60	54.5%
	Female	213	45.4%	316	49.0%	34	46.6%	84	39.3%		94	44.8%	170	51.4%		50	45.5%
Age	Mean (SD)	66.7 (10.0)		66.0 (9.0)		65.6 (10.2)		57.5 (9.8)		<0.001	67.4 (9.6)		69.3 (9.2)		0.020	68.3 (9.8)	
Stage	I	70	14.9%	65	10.1%	6	8.2%	46	21.5%	<0.001	20	9.5%	10	3.0%	0.001	2	1.8%
	II	399	85.1%	580	89.9%	67	91.8%	168	78.5%		190	90.5%	321	97.0%		108	98.2%
Location	Head of pancreas	287	61.2%	525	81.4%	56	76.7%	145	67.8%	<0.001	176	83.8%	252	76.1%	<0.001	70	63.6%
	Body of pancreas	25	5.3%	18	2.8%	8	11.0%	20	9.3%		27	12.9%	16	4.8%		0	0.0%
	Tail of pancreas	35	7.5%	47	7.3%	6	8.2%	16	7.5%		7	3.3%	27	8.2%		0	0.0%
	Other pancreas	122	26.0%	55	8.5%	3	4.1%	33	15.4%		0	0.0%	36	10.9%		40[1]	36.4%
Type of surgery	Pancreatico-duodenectomy	377	80.4%	571	88.5%	0	0.0%	149	69.6%	<0.001	200	95.2%	240	72.5%	<0.001	70	63.6%
	Other[2]	92	19.6%	73	11.3%	0	0.0%	65	30.4%		10	4.8%	91	27.5%		40	36.4%
	Unknown	0	0.0%	1	0.2%	73[3]	100.0%	0	0.0%		0	0.0%	0	0.0%		0	0.0%

[1]Includes tumours from body- and tail of pancreas
[2]Other types of pancreatectomy (e.g. total- and distal pancreatectomy or enucleation)
[3]Authors confirmed these patients underwent oncological resections

Table 2. Multivariable analyses of (neo-)adjuvant chemotherapy, 90-day mortality and overall survival.

			Use of neoadjuvant chemotherapy			Use of adjuvant chemotherapy			Ninety-day mortality			Overall survival		
			Odds ratio[1,2]	95% confidence interval	p-value	Odds ratio[1,2]	95% confidence interval	p-value	Odds ratio[3]	95% confidence interval	p-value	Hazard ratio[1]	95% confidence interval	p-value
National	Registry	BE	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		NL	0.48	0.29-0.89	0.020	0.70	0.53-0.93	0.012	0.56	0.35-0.89	0.014	1.11	0.96-1.28	0.177
		SLO	-	Not in analysis	-	0.32	0.19-0.56	<0.001	0.59	0.20-1.71	0.329	1.23	0.94-1.62	0.139
		UA	-	Not in analysis	-	-	Not in analysis	-	2.21	1.23-3.68	0.007	2.29	1.83-2.85	<0.001
	Sex	Male	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		Female	0.97	0.53-1.79	0.928	1.16	0.89-1.49	0.273	0.36	0.23-0.56	<0.001	0.77	0.68-0.87	<0.001
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		65-75 years	0.84	0.44-1.58	0.583	0.41	0.31-0.55	<0.001	2.01	1.25-3.26	0.004	1.16	1.01-1.34	0.040
		>75 years	0.40	0.13-1.20	0.101	0.08	0.05-0.12	<0.001	3.66	2.05-6.54	<0.001	1.75	1.44-2.12	<0.001
	Stage	I	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		II	0.55	0.26-1.18	0.126	4.68	3.11-7.04	<0.001	1.26	0.69-2.30	0.446	1.86	1.49-2.31	<0.001
Regional	Registry	CAT(E)	1.00	Reference	-	-	Not in analysis	-	1.00	Reference	-	1.00	Reference	-
		MU(D)	1.43	0.66-3.06	0.363	-	-	-	1.63	0.79-3.37	0.189	1.29	1.03-1.61	0.026
	Sex	Male	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		Female	0.92	0.45-1.88	0.821	1.36	0.87-2.12	0.181	0.87	0.50-1.68	0.671	1.01	0.81-1.25	0.929
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-

Table 2. Continued

		65-75 years	0.57	0.25-1.27	0.166	0.68	0.40-1.15	0.152	0.82	0.37-1.82	0.629	1.04	0.80-1.36	0.747
		>75 years	0.54	0.21-1.38	0.198	0.52	0.29-0.95	0.033	1.13	0.49-2.62	0.772	1.43	1.08-1.90	0.013
	Stage	I	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-	1.00	Reference	-
		II	0.51	0.14-1.83	0.299	2.61	0.54-12.72	0.235	2.05	0.27-15.71	0.489	1.29	0.80-2.09	0.304
Single center	Registry	MIL(I)	-	-	-	-	-	-	-	-	-	-	-	-
	Sex	Male	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		Female	1.10	0.38-3.16	0.859	1.04	0.40-2.72	0.936	-	-	-	0.82	0.53-1.27	0.365
	Age group	<65 years	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		65-75 years	0.75	0.24-2.32	0.617	0.19	0.04-0.94	0.194	-	-	-	0.99	0.59-1.66	0.965
		>75 years	0.30	0.06-1.56	0.151	0.04	0.01-0.19	<0.001	-	-	-	1.62	0.92-2.85	0.094
	Stage	I	1.00	Reference	-	1.00	Reference	-	-	-	-	1.00	Reference	-
		II	-	-	0.999	-	-	0.999	-	-	-	-	-	0.963

BE, Belgium; *NL*, The Netherlands; *SLO*, Slovenia; *UA*, Ukraine; *CAT(E)*, Catalonia (Spain); *MU(D)*, Munchen (Germany); *MIL(I)*, Milan (Italy)

[1]UA provided no data on adjuvant chemotherapy therefore excluded from analyses of national registries

[2]CAT(E) provided no data on adjuvant chemotherapy therefore excluded from analyses of regional registries

[3]Multivariable analyses in the single center registry was not possible due to low number of events

Multivariable analyses showed differences in odds ratios (OR) for the use of neo-ACT between the national registries: patients in NL were less likely to receive neo-ACT compared to BE (NL: OR=0.48, 95% CI=0.29-0.89, P=0.020, Table 2). No other predictive factors where identified in the national, regional or single center registries. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar OR.

Adjuvant chemotherapy

Overall, the use of ACT ranged from 40.5% in MU(D) - 70.0% in MIL(I). A higher proportion of ACT in stage II *versus* stage I was observed in all registries (Figure 1c-d). The proportion of patients with stage II receiving ACT varied between the national registries (*P*=0.017).

Multivariable analyses showed considerable differences in OR for the use of ACT between the national registries (Table 2). Patients in NL and SLO were significantly less likely to receive ACT compared to BE (NL: OR=0.70, 95% CI=0.53-0.93, *P*=0.012; SLO: OR=0.32, 95% CI=0.19-0.56, *P*<0.001). Furthermore, patients in ascending age group and patients with stage I were less likely to receive ACT in the national registries. In the regional- and single center registry patients in age group >75 years were also less likely to receive ACT. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar results, except that in regional –and single center registries each ascending age group was significantly less likely to receive ACT. Sensitivity analyses with 90-day mortality as covariate in the multivariable analyses showed similar OR.

Ninety-day mortality

Ninety-day mortality differed between the national registries (*P*=0.001, Figure 2). UA (13.6%) and MU(D) (8.5%) had the highest 90-day mortality in the national –and regional registries respectively, whereas overall MIL(I) (single center registry) had the lowest 90-day mortality (0.9%).

Multivariable analyses showed considerable differences in OR for 90-day mortality between the national registries (Table 2). Compared to BE, patients in NL had lower 90-day mortality (OR=0.56, 95% CI=0.35-0.89, *P*=0.014) and patients in UA (OR=2.21, 95% CI=1.23-3.68, *P*=0.007) had higher 90-day mortality. Female and younger age group were significant protective factors for 90-day mortality in the national registries. No predictive factors where identified in the regional registries. Multivariable analyses in the single center registry was not possible due to low number of events. Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar OR.

Overall survival

OS was significantly different in the national (*P*<0.001) and regional (*P*=0.005) registries (Figure 3a-c). In multivariable analysis for OS in the national registries, UA showed a significantly different OS compared to BE (Hazard Ratio (HR)=2.29, 95% CI=1.83-2.85, *P*<0.001, Table 2). Female sex was a significant protective factors for OS (HR=0.77, 95% CI=0.68-0.87, *P*<0.001). Patients in each ascending age group (65-75 years: HR=1.16, 95% CI=1.01-1.34, *P*=0.040; >75 years: HR=1.75, 95% CI=1.44-2.12, *P*<0.001) and stage II (HR=1.86, 95% CI=1.69-2.31, *P*<0.001) showed worse OS. In the regional registries, MU(D) showed a significantly different OS compared to CAT(E) (HR=1.29, 95% CI=1.03-1.61, P=0.026). Age group >75 years was a significant factor with worse OS compared to age group <65 years (HR=1.43, 95% CI=1.08-1.90, P=0.013), whereas age group 65-75 years was not. Also sex and stage were not significant factors for OS. In the single center registry, only age group >75 years was a borderline significant factor with worse OS compared to age group <65 years (HR=1.62, 95% CI=0.92-2.85, *P*=0.094).

In addition, median (95% CI) survival of patients who received ACT was: 20.1 (18.5-21.7) months in the national-, 19.0 (15.6-22.4) months in the regional-, and 30.0 (24.4-35.6) months in the single center registries and median (95% CI) survival of ACT naïve patients: 12.1 (10.3-13.9) months in the national-, 14.0 (11.2-16.8) months in the regional-, and 19.0 (11.1-26.8) months in the single center registries, although a direct comparison is not possible.

Sensitivity analyses with patients with 'unknown' stage added to the multivariable analyses showed similar HR. Sensitivity analyses with ACT added to the multivariable analyses showed similar HR.

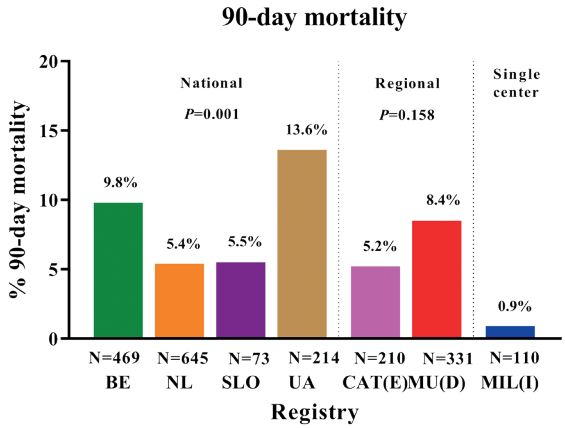

Figure 2. Ninety-day mortality rates per registry.

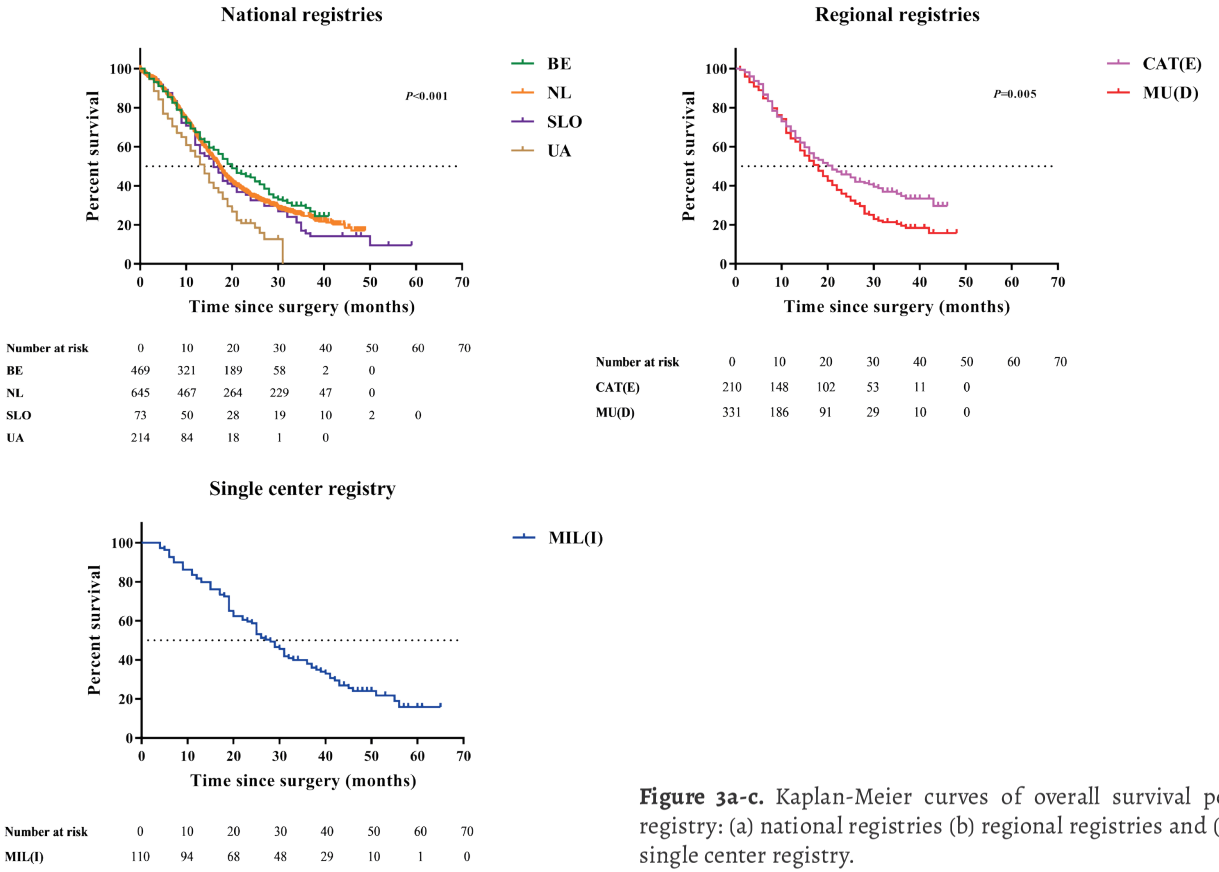

Figure 3a-c. Kaplan-Meier curves of overall survival per registry: (a) national registries (b) regional registries and (c) single center registry.

DISCUSSION

The main aim of this study was to describe and compare (neo–)ACT and outcomes of patients who underwent tumor resection for stage I & II pancreatic adenocarcinoma in the EURECCA consortium. There were some differences in the use of neo-ACT. Although the ESMO guidelines, during the study period and most recent, recommended the use of ACT, variations were observed in OR for ACT usage between national registries.[6] Also large variations in 90-day mortality and OS were observed between the registries included in this study.

Previous studies from the EURECCA consortium showed variations in the use of chemo(radiation)therapy in colon-, rectal- and breast cancer patients.[17-19] The observed variations in neo-ACT, but mainly ACT, between the registries in this study are in concordance with a recent large-scale international study of resected PC patients.[20] A possible explanation for the variations can be differences in adherence to (inter)national guidelines.[18,19] Also, cultural, socioeconomic and health-care differences may play a role in the use of (neo-)ACT.[21-23] The observation that few patients received neo-ACT was probably due to the statement by the ESMO guidelines (during the study period) that neo-ACT should be used in clinical trial settings.[6] Clinical trials are more easily accessible in specialized centers which explains the greater use of neo-ACT in the (specialized) single center registry compared to the national –and regional registries. A recent meta-analysis has shown the benefit of neo-ACT over upfront surgery.[24] An interesting international comparison would be how these results are implemented in more recent practice. A complicated postoperative course can delay or omit the use of ACT.[25] In a sensitivity analyses with 90-day mortality added to the multivariable analyses for the use of ACT, we confirmed that differences in 90-day mortality were not of influence on the differences in the use of ACT between the registries. The use of ACT decreased per ascending age group and patients in age group >75 years showed a significant worse OS in multivariable analyses in the national, regional –and single center registries. As previously investigated, elderly patients are at higher risk of postoperative complications.[26] Although centralization improved outcome of pancreatic surgery in elderly patients in a recent study, further research is needed to gain knowledge on this matter.[27]

Variations in 90-day mortality were observed between the national registries, even after adjustment for sex, age group and stage. Multiple studies have shown a lower postoperative mortality after pancreatic surgery in high- compared to low-volume hospitals.[28,29] In our study this could not be assessed, because the annual hospital volumes were not available. Nonetheless, BE and MU(D) showed a high 90-day mortality and centralization of pancreatic surgery was not implemented there during the study

period. Caution has to be taken with this statement as detailed information about perioperative treatment, likely to affect 90-day mortality, was not available.

This study showed a better survival in patients receiving ACT compared to naïve patients in the national, regional –and single center registries. This can very well be explained by confounding by indication (fit patients with a good prognosis are generally more likely to receive ACT) and therefore a justifiable comparison is not possible. The recent ESPAC-4 trial (2017), showed a significant better survival for patients treated with adjuvant gemcitabine and capecitabine compared to gemcitabine alone (28.0 (95% CI=23.5-31.5 months *versus* 25.5 (95%CI=22.7-27.9) months) after resection for PC.[7] Considering the randomized ESPAC-trial has strict inclusion criteria (e.g. full recovery after surgery, creatinine clearance ≥50 mL/min) and our study is mainly population-based, the results are largely comparable. Still, direct comparison is hampered by the differences in study design. In a sensitivity analyses with (neo-)ACT added to the multivariable analyses for OS, we confirmed that differences in ACT were not of influence on the differences in OS between the registries. Definite conclusions cannot be drawn from this sensitivity analysis since immortal time bias and confounding by indication cannot be ruled out.

Our study has several limitations. First, caution has to be taken with interpretation of the results as differences in (unmeasured) patient characteristics (e.g. patient selection for tumor resection) might have been of influence. Nevertheless, analyses were adjusted for important factors (sex, age group, stage) and still showed differences between the registries. Second, due to inherent differences between national, -regional and single center registries, which also explain the observed inter-registry-type variations, analyses had to be performed separately per registry type and lowered the statistical power (e.g. multivariable analyses for 90-day mortality was not possible in the single center registry). Third, due to missing data this study excluded some patients (e.g. 'unknown' stage or tumor resection) and registries (e.g. SLO and UA did not provide data on neo-ACT, CAT(E) and UA did not provide data on ACT and the dataset from BG could not confirm tumor resection) from certain analyses. A possible explanation for this is that the provided datasets may originally have been established for other intentions (e.g. Cancer Registry or Clinical/Surgical Audit) and thus focussed on completeness of certain (other) variables. Although most included registries are surgically driven and therefore very comparable, this probably introduced missing data bias.[30] Sensitivity analyses with patients with 'unknown' stage added to the analyses confirmed the robustness of the results of this study. Still, variables as stage and tumor resection are pivotal when investigating treatment and outcome in cancer patients. Future registration should focus on completeness and uniform use of definitions as previously stated by other member of the EURECCA consortium.[13,17] Nonetheless, this study is the first in describing

and comparing (neo-)ACT and outcome of patients undergoing tumor resection for pancreatic adenocarcinoma stage I & II in eight different European registries.

In conclusion, the results of this study give a clear insight in the clinical practice of the partners in the EURECCA Pancreas consortium. Overall, the variations illustrate the difference in implementation of universally accepted and used guidelines for treatment of pancreatic adenocarcinoma stage I & II. The differences in the use of (neo-)ACT and outcome provide us the chance to further investigate the *best practices*. Moreover, the EURECCA Pancreas consortium underlines the need for uniform registration as international comparisons will become increasingly important pillars of international guidelines.

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SUPPLEMENTARY MATERIAL

Table S1. Description of registries.

	Registry							
	National					**Regional**		**Single center**
	Belgium	**The Netherlands**	**Slovenia**	**Bulgaria**	**Ukraine**	**Catalonia**	**Munich**	**Milan**
Registry	BCR: Belgian Cancer Registry	NCR: Netherlands Cancer registry	Cancer Registry of Republic of Slovenia	BNCR: Bulgarian National Cancer Registry	NCRU: National Cancer Registry of Ukraine	Pancreatic Surgery Clinical Audit Catalonia	MCR: Munich Cancer Registry	ICH pancreatic surgery registry
Organisation	Population based	Cancer registry	Population based	Population based	Regions and central database	Clinical audit	Clinical Cancer Registry	Surgical Audit
Inhabitants (x10^6)	11	17	2	7.3	45	7.5	4.7	3.2
Incidence years in provided dataset	2004-2013	2010-2013	2012-2014	2012-2013	2012-2013	2012-2013	2010-2014	2010-2017
Coverage of national, regional or single center data	>98%	>95%	>95%%	95%	100%	100%	>95%	100%
Collection of data	Per center, data managers, pathology laboratories and use of medical claims data	Per center, data manager	Per center, data manager	13 regional centers, 1 central database	Regional center, registrars	Per center, data manager	Central data management of information provided from cancer units	Surgical staff

Table S1. Continued

Collection of survival data until	01-07-2015	01-02-2016	01-06-2017	12-01-2016	19-02-2015	01-01-2016	15-04-2016	03-08-2017
Centralisation of surgery	No	20 hospitals	2 hospitals	No	40 hospitals	10 hospitals	27 hospitals, 60% in 4 hospitals	Not applicable

Table S2. Patient & tumor characteristics from Bulgaria.

		Registry	
		National	
		Bulgaria (*N*=2496)	
	N	**%**	
Sex	**Male**	1439	57.7%
	Female	1057	42.3%
Age	**Mean (SD)**	68.1 (11.3)	
Year of diagnosis	**2012**	1240	49.7%
	2013	1256	50.3%
Stage	**0**	0	0.0%
	I	120	4.8%
	II	334	13.4%
	III	302	12.1%
	IV	1130	45.3%
	Unknown	610	24.4%
Location	**Head of pancreas**	1220	48.9%
	Body of pancreas	272	10.9%
	Tail of pancreas	140	5.6%
	Other pancreas	864	34.6%
Pathology	**Carcinoma non classified**	1187	47.6%
	Adenocarcinoma	1160	46.5%
	Neuro-endocrine	30	1.2%
	Cystic / mucinous / serous	78	3.1%
	Other[1]	41	1.6%
	Unknown	0	0.0%
Surgery[2]	**No**	1658	66.4%
	Yes	838	33.6%

[1]Includes e.g.: squamous cell carcinoma, melanoma (metastatic), liposarcoma, leiomyosarcoma, lymphomas, Gastrointestinal Stromal Tumor, pancreatoblastoma
[2]Tumor resection could not be confirmed

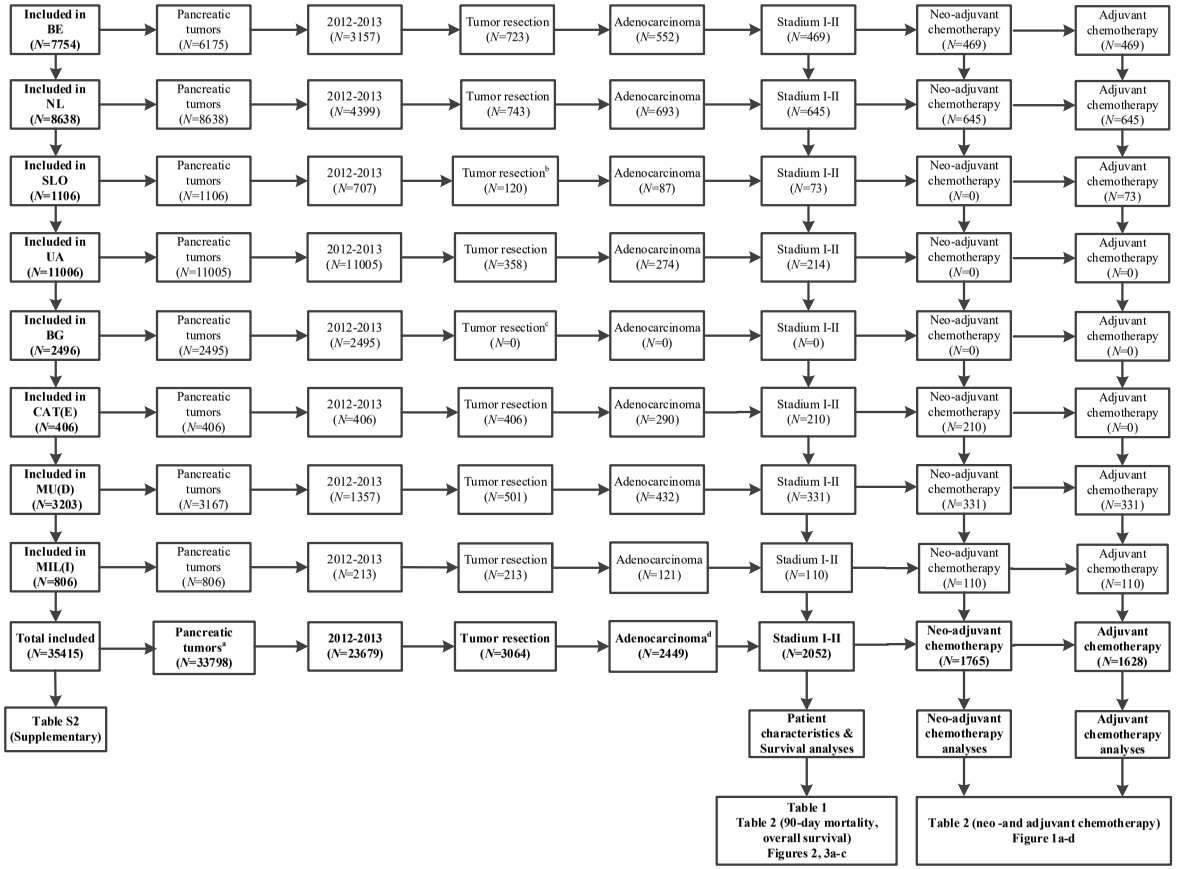

Figure S1. Flow chart of inclusion of patients per registry. [a]Included: C25.0-C25.9; excluded: C25.4.[14] [b]Includes only oncological resections. [c]Unable to confirm if patients underwent tumor resection and therefore only used in patient & tumor characteristics description.[d] Included: 8140-8380, 8500-8585; excluded: 8150-8158, 8240-8249.[14]

CHAPTER 3

Treatment and survival of elderly patients with stage I-II pancreatic cancer: a report of the EURECCA Pancreas Consortium

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ABSTRACT

Background: Elderly patients with pancreatic cancer are underrepresented in clinical trials resulting in a lack of evidence. The aim of this study was to compare treatment and overall survival (OS) of patients ≥70 years with stage I-II pancreatic cancer in the EURECCA Pancreas Consortium.

Methods: This was an observational cohort study of the Belgian (BE), Dutch (NL) and Norwegian (NOR) cancer registries. The primary outcome was OS. Secondary outcomes were resection, 90-day mortality after resection, and (neo)adjuvant and palliative chemotherapy.

Results: In total, 3624 patients were included. Resection (BE: 50.2%; NL: 36.2%; NOR: 41.3%; P<0.001), use of (neo)adjuvant chemotherapy (BE: 55.9%; NL: 41.9%; NOR: 13.8%; P<0.001) and palliative chemotherapy (BE: 39.5%; NL: 6.0%; NOR: 15.7%; P<0.001) differed. Ninety-day mortality differed (BE: 11.7%; NL: 8.0%; NOR: 5.2%; P<0.001). Median OS in patients with resection (BE: 17.4; NL: 15.9; NOR: 25.4 months; P<0.001) and in patients without resection (BE: 7.0, NL: 3.9, NOR: 6.5 months; P<0.001) differed.

Conclusions: Differences were observed in treatment and OS in patients ≥70 years with stage I-II pancreatic cancer between the population based cancer registries. Future studies should focus on selection criteria for (non)-surgical treatment in older patients, so that clinicians can tailor treatment.

INTRODUCTION

For pancreatic cancer, very little progress has been made in terms of mortality rates over the past decades.[1] Resection combined with systemic treatment offers the best chance for prolonged survival. Resectability is mainly determined by contact between the tumor and the venous and arterial vasculature.[2] Patients with stage I-II pancreatic cancer are generally considered eligible for resection. Unfortunately, about 20% of all patients are resectable due to advanced or metastatic disease at diagnosis.[3] Still, even after tumor resection of stage I-II pancreatic cancer, prognosis is poor with a median overall survival (OS) of 17-30 months.[4]

The most recent European Society of Medical Oncology (ESMO) guideline does not consider advanced age a contra-indication for resection, but states that comorbidities and poor functional status can be a reason to refrain from resection.[5] The National Comprehensive Cancer Network (NCCN) guideline is largely similar to the ESMO guideline.[6] Although no statements are made regarding advanced age directly, the guideline states that performance status should be taken into account when considering treatment strategy. Older cancer patients are often underrepresented in clinical trials, possibly due to the strict inclusion criteria.[7] Recently, a study with population-based data of multiple pancreatic cancer registries, showed that the median age at diagnosis is 70 years.[8] This clearly differs from large randomized controlled trials in pancreatic cancer in which the median age is 61-65 years.[9-12] There is a lack of evidence on treatment and survival of elderly patients with pancreatic cancer.

The EUropean REgistration of Cancer CAre (EURECCA) consortium, established by the European CanCer Organisation (ECCO), investigates differences in treatment and outcomes of patients in a real world scenario by using cancer registry data.[13] Previous studies from the EURECCA Pancreas Consortium showed considerable variations in treatment and outcomes.[14,15]

The aim of this study was to compare treatment strategies and survival outcomes of patients ≥70 years with stage I-II pancreatic cancer in the Belgian (BE), Dutch (NL) and Norwegian (NOR) national cancer registries from the EURECCA Pancreas Consortium.

METHODS

Design and patient selection

This is an observational cohort study of three cancer registries in the EURECCA Pancreas Consortium reported according to the STROBE criteria.[16] The BE, NL and NOR national cancer registries were selected because of data quality, data availability and similarity regarding design and organization (Table S1; Supplementary Material). Also cancer incidence and life expectancy are largely similar between the national cancer registries.[17] Patients ≥70 years with pancreatic adenocarcinoma stage I-II, diagnosed from 2012 through 2016 (2012 through 2015 for BE), were included. Patients ≥70 years were included according to the definitions of 'elderly' of the International Society of Geriatric Oncology (http://siog.org/content/defining-elderly). An overview of stage distribution per cancer registry is provided in Table S2 (Supplementary Material). Patients with other malignancies were not excluded, because pancreatic cancer is often determinative for the prognosis. In case of synchronous pancreatic cancer, the tumor with the highest known stage was used.

Data collection, definition and preparation

Anonymous data obtained from the cancer registries were: 1) patient and tumor related variables: sex, age, tumor topography, tumor morphology, tumor stage; 2) treatment related variables: tumor resection, chemotherapy, radiotherapy; and 3) outcome related variables: vital status, follow-up.

Patients were divided into age groups: 70-74, 75-79 and ≥80 years. The International Classification of Disease for Oncology (ICD-O-3) was used for tumor topography and morphology.[18] Pancreatic cancer were identified through tumor topography codes (C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, C25.9) and morphological codes (8000-8009, 8010-8012, 8014-8049, 8050-8089, 8140-8149, 8154, 8158, 8159, 8161, 8163-8169, 8171-8179, 8181-8239, 8244-8245, 8250-8311, 8313-8389, 8440-8499, 8500-8549, 8550-8559, 8560-8579). For NOR, also morphological codes 690099 and 699999 (no or unknown microscopic examination) were included, since similar patients are coded as 8000 in the BE and NL cancer registry. Unless patients with codes 690099 and 699999 were diagnosed by death certificate only, these patients are not included in the BE and NL cancer registry.

The seventh edition of the TNM classification was in use during the study period and was therefore used for tumor staging in BE and NL.[19] The pTNM stage was used in patients who underwent tumor resection and the cTNM stage was used in patients who did not undergo tumor resection. In case of missing pTNM stage variables for patients who underwent tumor resection, cTNM stage variables were used when available. In NOR tumor stage was categorized as localized, regional or distant disease. For analyses,

localized and regional tumor disease were included. In case of missing data on tumor resection, chemotherapy and radiotherapy it was considered as 'no'. No distinction was made between neo- and adjuvant non-surgical treatment since this data was not available for NOR. OS was calculated from the day of diagnosis or tumor resection until the date of death or last follow-up.

Outcomes and comparisons

The primary outcome was OS. Secondary outcomes were tumor resection and 90-day mortality after tumor resection, use of non-surgical treatment strategies ((neo)adjuvant and palliative chemotherapy and radiotherapy). The main comparison was focused at assessing differences in the three cancer registries. Subgroup analyses were performed comparing per age group between the cancer registries (in case of ≥60 events).

Statistical analyses

Statistical analyses were performed using SPSS Inc. for Windows (version 23.0). Categorical data were reported as numbers (percentages) and compared using the Chi square test. Multivariable binary logistics regression was used to assess predictive factors (cancer registry, age group) for tumor resection and 90-day mortality after tumor resection and use of non-surgical treatment strategies ((neo)adjuvant and palliative chemotherapy and radiotherapy) (in case of ≥60 events). Survival analyses were performed separately for patients who underwent tumor resection and patients who did not undergo tumor resection. Kaplan-Meier curves were used to estimate median OS and the 95% confidence interval (CI) and log-rank tests were used to compare OS. Multivariable Cox regression were used to assess predictive factors (cancer registry, age group) for OS. BE and age group 70-74 were the reference categories in the multivariable analyses. Sensitivity analyses were performed, excluding patients who deceased within 90 days after tumor resection or diagnosis and including chemotherapy as additional factor to assess the influence on OS and minimize confounding by indication. In patients who did not undergo tumor resection, a sensitivity analysis was performed only with patients in which the tumor was pathologically confirmed. The original results were considered robust if the sensitivity analyses showed similar results. A $P<0.05$ was considered as statistically significant for all analyses.

RESULTS

Patient and tumor characteristics

In total, 3624 patients were included: 1002 (27.6%) from BE, 1973 (54.4%) from NL, and 649 (17.9%) from NOR (Table 1). Distribution of sex was comparable between the cancer registries. Age group distribution was largely similar. Most tumors were stage II/ regional stage (72.1% in BE; 67.4% in NL; 72.0% in NOR).

Table 1. Patient and tumor characteristics by cancer registry.

		Cancer registry					
		BE		NL		NOR	
		N	%	N	%	N	%
Total		**1002**	**27.6**	**1973**	**54.4**	**649**	**17.9**
Age group	**70-74**	300	29.9	545	27.6	216	33.3
	75-79	310	30.9	564	28.6	166	25.6
	≥80	392	39.1	864	43.8	267	41.1
Sex	**Male**	458	45.7	894	45.3	295	45.5
	Female	544	54.3	1079	54.7	354	54.5
Stage[a]	**IA**	79	7.9	158	8.0	182	28.0
	IB	201	20.1	485	24.6		
	IIA	226	22.6	552	28.0	467	72.0
	IIB	496	49.5	778	39.4		

[a]For NOR, no distinction was made for stage IA/IB and IIA/IIB.

Treatment strategies

Tumor resection

The tumor resection rate differed between the cancer registries: 50.2% in BE, 36.2% in NL, and 41.3% in NOR (P<0.001; Figure 1A). Subgroup analysis showed a similar tumor resection rate in age group 70-74 (P=0.424) and different tumor resection rates in the higher age groups between the registries (both P<0.001).

In multivariable analyses, patients in NL (OR=0.54, 95% CI=0.46-0.65) and NOR were less likely (OR=0.65, 95% CI=0.52-0.81) to undergo tumor resection compared to BE (Table 2). Patients in age group 75-79 (OR=0.61, 95% CI=0.51-0.73) and age group ≥80 (OR=0.10, 95% CI=0.09-0.13) were less likely to undergo tumor resection compared to age group 70-74.

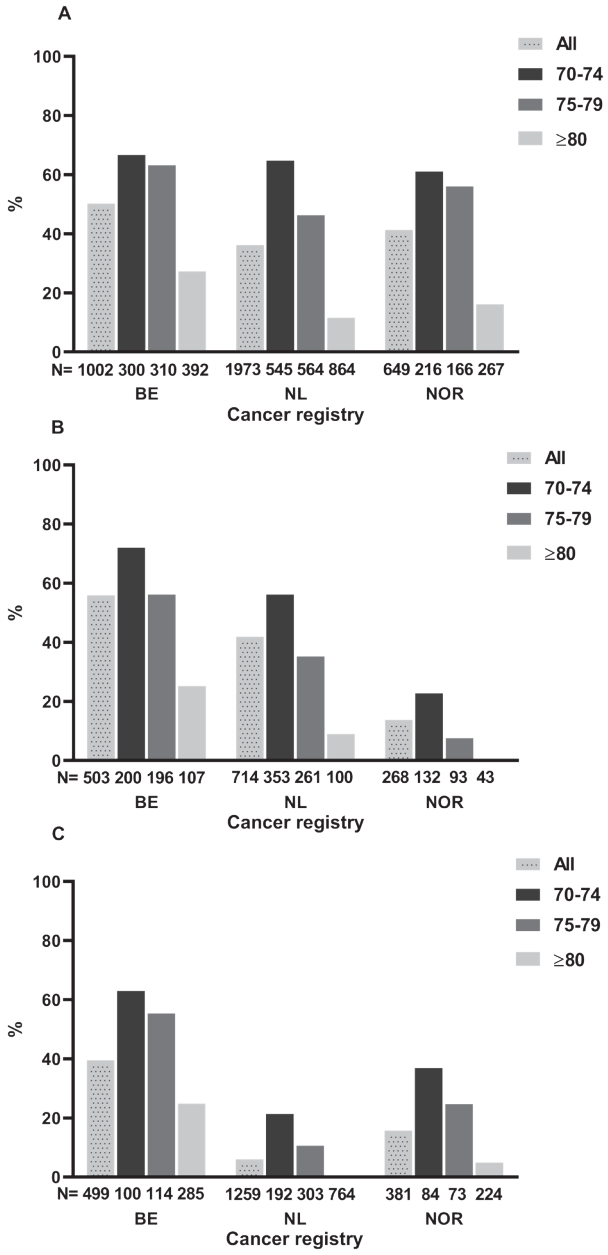

Figure 1 A-C. Treatment strategies: (A) tumor resection by cancer registry and age group, (B) (neo-)adjuvant chemotherapy by cancer registry and age group, (C) palliative chemotherapy by cancer registry and age group.

Table 2. Multivariable analyses for treatment strategies.

		Tumor resection[a]		(Neo)adjuvant chemotherapy[b]		Palliative chemotherapy[c]	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Cancer registry	**BE**	**Reference**		**Reference**		**Reference**	
	NL	0.54 (0.46-0.65)	<0.001	0.43 (0.34-0.56)	<0.001	0.08 (0.05-0.10)	<0.001
	NOR	0.65 (0.52-0.81)	<0.001	0.09 (0.06-0.13)	<0.001	0.22 (0.15-0.32)	<0.001
Age group	**70-74**	**Reference**		**Reference**		**Reference**	
	75-79	0.61 (0.51-0.73)	<0.001	0.43 (0.34-0.55)	<0.001	0.54 (0.38-0.75)	<0.001
	≥80	0.10 (0.09-0.13)	<0.001	0.10 (0.07-0.15)	<0.001	0.10 (0.07-0.14)	<0.001

OR: odds ratio; CI: confidence interval
[a]Tumor resection in the total cohort (N=3624).
[b]Chemotherapy before or after tumor resection or both (N=1485).
[c]Chemotherapy in patients who did not undergo tumor resection (N=2139).

Non-surgical treatment in patients who underwent tumor resection

The use of (neo)adjuvant chemotherapy differed between the cancer registries: 55.9% in BE, 41.9% in NL and 13.8% in NOR (P<0.001; Figure 1B). Subgroup analysis showed that in all age groups the use of (neo)adjuvant chemotherapy differed between the cancer registries (all P<0.001). In multivariable analyses, patients in NL (OR=0.43, 95% CI=0.34-0.56) and NOR (OR=0.09, 95% CI=0.06-0.13) were less likely to receive (neo)adjuvant chemotherapy compared to BE (Table 2). Patients in age group 75-79 (OR=0.43, 95% CI 0.34-0.55) and age group ≥80 (OR=0.10, 95% CI=0.07-0.14) were less likely to receive (neo)adjuvant chemotherapy compared to age group 70-74.

The use of (neo)adjuvant radiotherapy was similar between the cancer registries: 4.0% in BE, 2.2% in NL, and 3.7% in NOR (P=0.183).

Non-surgical treatment in patients who did not undergo tumor resection

The use of palliative chemotherapy differed between the cancer registries: 39.5% in BE, 6.0% in NL and 15.7% in NOR (P<0.001; Figure 1C). Subgroup analysis showed that in all age groups the use of palliative chemotherapy differed between the cancer registries (all P<0.001). In multivariable analyses, patients in NL (OR=0.08, 95% CI=0.05-0.10) and NOR (OR=0.22, 95% CI=0.15-0.32) were less likely to receive palliative chemotherapy compared to BE (Table 2). Patients in age group 75-79 (OR=0.54, 95%CI=0.38-0.75) and age group ≥80 (OR=0.10, 95% CI=0.07-0.15) were less likely to receive palliative chemotherapy compared to age group 70-74.

The use of palliative radiotherapy differed between the cancer registries: 7.4% in BE, 1.6% in NL, and 0.7% in NOR (P<0.001).

Survival

Ninety-day mortality after tumor resection

Ninety-day mortality after tumor resection differed between the cancer registries: 11.7% in BE, 8.0% in NL, and 5.2% in NOR (P<0.001; Figure 2). Subgroup analysis showed different 90-day mortality after tumor resection in age group 70-74 (P=0.012) and similar 90-day mortality after tumor resection in age group 75-79 (P=0.138) and age group ≥80 (P=0.324) between the cancer registries. In multivariable analyses, patients in NL (OR=0.64, 95% CI=0.43-0.95) and NOR (OR=0.38, 95% CI=0.20-0.72) were less likely to experience 90-day mortality after tumor resection compared to BE (Table 3). Age group was not a significant predictive factors for 90-day mortality after tumor resection.

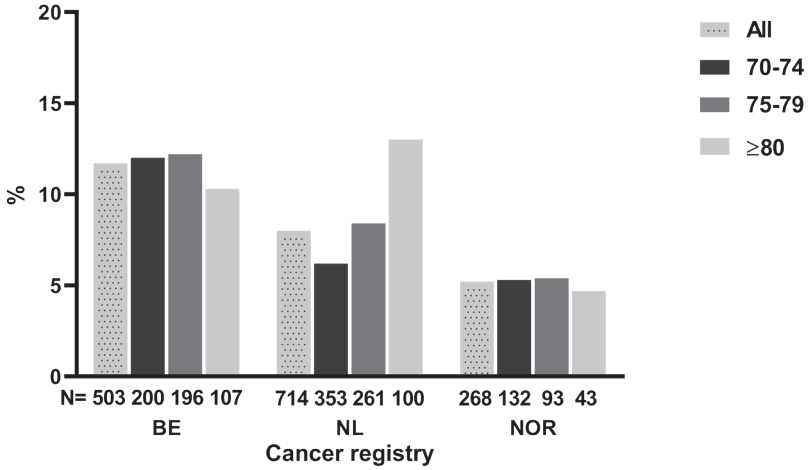

Figure 2. Ninety-day mortality after tumor resection by cancer registry and age group.

Overall survival of patient who underwent tumor resection

Median OS in patients who underwent tumor resection differed between the cancer registries: 17.4 (15.3-19.4) months in BE, 15.9 (14.4-17.5) months in NL, and 25.4 (21.6-29.2) months in NOR (P<0.001; Figure 3A). Subgroup analysis showed different OS in age group 70-74 between the cancer registries and similar OS in age group 75-79 and age group ≥80 (Figure S1A-C). In multivariable analyses, patients in NL showed similar OS (HR=1.07, 95% CI=0.93-1.22) and patients in NOR showed better OS (HR=0.72, 95% CI=0.60-0.87) compared to BE (Table 3). Patients in age group 75-79 (HR=1.23, 95% CI 1.07-1.40) and age group ≥80 (HR=1.30, 95% CI=1.10-1.54) showed worse OS compared to age group 70-74.

In the sensitivity analysis without patients who deceased within 90 days after tumor resection, patients who received (neo)adjuvant chemotherapy showed better OS compared to (neo)adjuvant chemotherapy naïve patients and the results for cancer registry and age group were robust (Table 4 and Table S3, Supplemental Material). Detailed analyses by cancer registry and age group showed inconsistent results of OS of patients who received (neo)adjuvant chemotherapy versus (neo)adjuvant chemotherapy naïve patients (Table S4, Supplemental Material).

Overall survival of patients who did not undergo tumor resection

Median OS in patients who did not undergo tumor resection differed between the cancer registries: 7.0 (6.2-7.8) months in BE, 3.9 (3.5-4.3) months in NL, and 6.5 (5.0-8.0) months in NOR (P<0.001; Figure 3B). Subgroup analysis showed different OS in all age groups between the cancer registries (Figure S2A-C). In multivariable analyses, patients in NL (HR=1.46, 95% CI=1.31-1.62) and NOR (HR=1.35, 95% CI=1.18-1.55) showed worse OS compared to BE (Table 3). Patients in age group 75-79 showed similar (HR=1.12, 95% CI 0.97-1.29) and age group ≥80 showed worse OS (HR=1.28, 95% CI=1.14-1.44) compared to age group 70-74.

In the sensitivity analysis without patients who deceased within 90 days after diagnosis, patients who received palliative chemotherapy did not show better OS compared to palliative chemotherapy naïve patients and the results for cancer registry and age group were robust (Table 4 and Table S3, Supplemental Material). Detailed analyses by cancer registry and age group showed inconsistent results of OS of patients who received palliative chemotherapy versus palliative chemotherapy naïve patients (Table S4, Supplemental Material). In the sensitivity analysis, with patients in which the tumor was pathologically confirmed, results regarding cancer registries, age group and palliative chemotherapy were robust.

Table 3. Multivariable analyses for survival.

		90-day mortality after tumor resection[a]		Overall survival of patients who underwent tumor resection[b]		Overall survival of patients who did not undergo tumor resection[c]	
		OR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cancer registry	**BE**	Reference		Reference		Reference	
	NL	0.67 (0.45-0.98)	0.040	1.07 (0.93-1.22)	0.340	1.46 (1.31-1.62)	<0.001
	NOR	0.42 (0.23-0.77)	0.005	0.72 (0.60-0.87)	0.001	1.35 (1.18-1.55)	<0.001
Age group	**70-74**	Reference		Reference		Reference	
	75-79	1.18 (0.79-1.76)	0.433	1.23 (1.07-1.40)	0.001	1.12 (0.97-1.29)	0.111
	≥80	1.30 (0.79-2.13)	0.307	1.30 (1.10-1.54)	0.002	1.28 (1.14-1.44)	<0.001

OR: odds ratio; CI: confidence interval; HR: hazard ratio
[a]Ninety-day mortality in patients who underwent tumor resection (N=1485).
[b]Overall survival of patients who underwent tumor resection (N=1485).
[c]Overall survival of patients who did not undergo tumor resection (N=2139).

Table 4. Sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, by age group and treatment strategy.

					Age group								
Treatment strategy	**Total**			**70-74**			**75-79**			**≥80**			
	N	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**
Tumor resection + (neo)adjuvant chemotherapy	602	23.2	22 (19-25)	366	41.6	24 (20-28)	200	24.8	20 (18-23)	36	3.9	21 (13-30)
Tumor resection alone	752	28.9	18 (17-20)	266	30.3	22 (18-26)	298	37.0	16 (14-18)	188	20.5	17 (15-19)
Palliative chemotherapy	293	11.3	9 (8-11)	118	13.4	11 (9-13)	101	12.5	7 (2-12)	74	8.1	10 (8-11)
No treatment	951	36.6	8 (7-9)	129	14.7	12 (10-13)	205	25.5	8 (7-9)	617	67.4	8 (7-9)
Total	**2599**	**100**	**13 (12-14)**	**879**	**100**	**18 (17-20)**	**805**	**100**	**14 (12-15)**	**915**	**100**	**10 (9-10)**

[a]Median overall survival in months after tumor resection (patients who underwent tumor resection) or after diagnosis (patients who did not undergo tumor resection) and 95% confidence interval

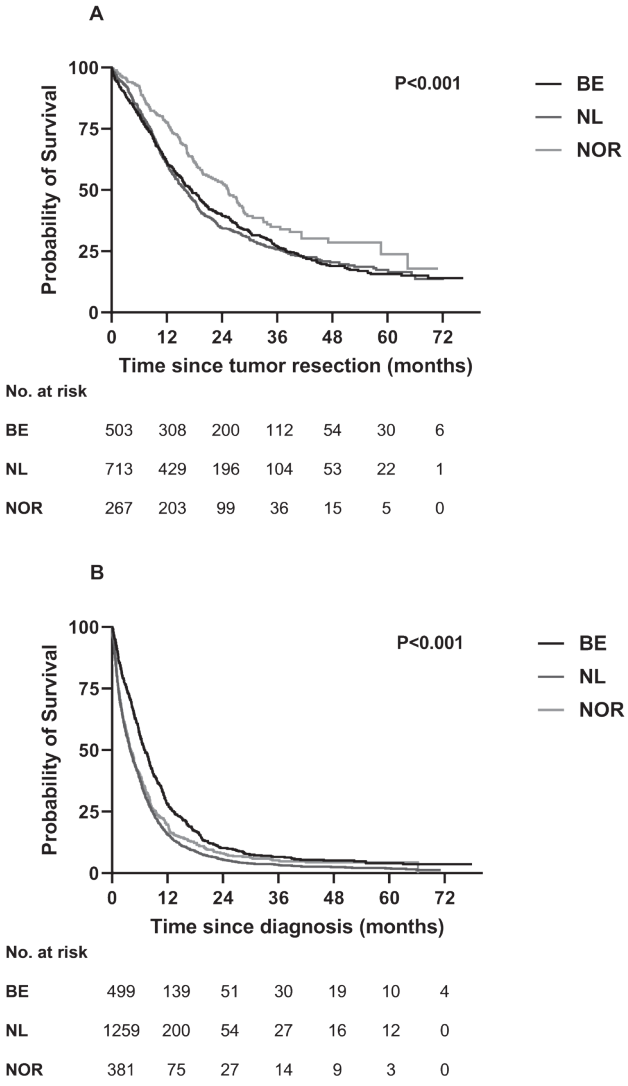

Figure 3 A-B. Overall survival by cancer registry: (A) patients who underwent tumor resection, (B) patients who did not undergo tumor resection.

DISCUSSION

In this study, treatment and survival of patients ≥70 years with stage I-II pancreatic cancer were evaluated in three European population based cancer registries. Variations were observed for tumor resection rate (ranging 36-50%), (neo)adjuvant chemotherapy (ranging 14-56%) and palliative chemotherapy (ranging 6-40%). Subgroup analysis showed

that patients in the age group 70-74 had a similar tumor resection rate between the cancer registries, which was different in the older age groups. The use of (neo-)adjuvant and palliative chemotherapy was different in all age groups between the cancer registries. The use of (neo-)adjuvant and palliative radiotherapy was low. Ninety-day mortality after tumor resection was lower in NL and NOR compared to BE. In patients who underwent tumor resection, OS in NOR was better compared to BE and NL was similar to BE. Overall, a better OS was observed in patients who received (neo)adjuvant compared to chemotherapy naïve patients. In patients who did not undergo tumor resection, OS in BE was better compared to NL and NOR.

Although the TNM staging system is not directly translatable to widely used resectability criteria[5], the low resection rate in this study, compared to previously reported[20], is noteworthy and could be explained by the inclusion of patients ≥70 years. Also, some patients with may have anatomically resectable disease, yet have unfavourable biological (high CA19.9) and conditional (poor functional status) factors.[21] An important observation is that only in the age group 70-74 tumor resection rate was similar between the cancer registries. According to the ESMO and NCCN guideline, a poor functional status, and not advanced age only, can be a good reason to be more retained by clinicians or patients.[5,6] Unfortunately, no data (e.g. ASA, ECOG score) were available to investigate this. Variation between the cancer registries regarding the cultural factors that influence the decision making for treatment in elderly patients might also be an explanation.[22,23] Despite the higher tumor resection rates in BE and NOR in the older age groups, which could have illustrated poor patient selection, 90-day mortality after resection was similar. Only in NL, 90-day mortality after resection increased with ascending age groups. Possibly the transparent outcome indicators (mortality) in the Dutch Pancreatic Cancer Audit[24], refrains clinicians in NL in performing more tumor resections. A recent meta analyse showed elderly patients have more comorbidities, more overall complications (mainly respiratory), though a comparable mortality compared to younger patients.[25] Adequate patient selection, prehabilitation, enhanced recovery protocols, and centralization of pancreatic surgery for elderly patients might improve outcomes.[26-30] Others have advocated a multidisciplinary approach to high-risk elderly patients undergoing major surgery.[31] Several studies have illuminated the importance of geriatric assessment to improve outcomes of cancer treatment.[32,33] However, high level evidence of functional recovery of elderly patients undergoing pancreatic surgery is lacking. Surprisingly, age was not a predictive factor for functional recovery in a Canadian population-based cohort study.[34]

The use of (neo)adjuvant chemotherapy was different between the cancer registries, comparable with previous international studies.[8,15] Still, this is notable since adjuvant chemotherapy is the standard treatment.[5,6] Morbidity after surgery is not uncommon in

elderly patients and may cause omission of chemotherapy.[25,26,35] Unfortunately, these data were not available in present study. No distinction was made between neo- and adjuvant chemotherapy because NOR did not provide this. This was accepted since the use of neoadjuvant therapy was expected to be low, as the ESMO and NCCN guidelines stated that neoadjuvant therapy should be used in clinical trials and elderly patients are often not included. The sensitivity analyses showed that the differences between the cancer registries in OS after tumor resection cannot be explained by the differences in the use of (neo)adjuvant chemotherapy. It remains unknown which other factors also contribute to the differences in OS.

The largest observed difference was in the use of palliative chemotherapy between BE (40%) and NL (6%). This can be explained by the fact that the ESMO and NCCN guidelines state that palliative treatment can be considered depending on the performance status of the patient.[5] Differences can also be explained by variations in nihilistic attitudes of clinicians and patients regarding the small benefit of palliative chemotherapy in elderly pancreatic cancer patients.[36] Multiple randomized controlled trials showed improved OS and quality of life with palliative chemotherapy, but adverse events are not rare.[9,10] Exemplified by the present study, results from randomized controlled trials cannot directly be extrapolated to the elderly population due to the strict inclusion criteria. These factors should be discussed with the patient before a shared decision on treatment strategy can be made. In the sensitivity analyses, patients from BE had a better OS compared to NL and similar to NOR, which suggests that the differences in the use of palliative chemotherapy do not explain the observed differences in OS. Furthermore, palliative chemotherapy was not a significant predictive factor for OS in sensitivity analyses. The unclear pattern between (neo)adjuvant and palliative chemotherapy and OS in subgroup analyses suggests that better patient selection is needed to improve resource utilization and OS. But the results also show that tumor resection, (neo)adjuvant and palliative chemotherapy, in correctly selected patients, can provide prolonged survival.

This study has several limitations. First, although the design and organization of the national cancer registries was similar, differences in the completeness of data and patients, which could have influenced the baseline characteristics and results, have to be considered. Baseline characteristics are of paramount importance for external validity of study results and should be studied carefully.[17,37] Our findings may possibly be influenced by differences in (under)-registration of elderly patients with pancreatic cancer.[38] On the other hand, age distribution was similar in the cancer registries. Furthermore, the number of included patients per cancer registry was similar to the expected amount of patients based on the size of the cancer registry population, incidence of pancreatic cancer and the provided incidence years. The proportion of 'unknown' stage differed between the cancer registries. We hypothesized that this only marginally has influenced

our results. The majority of patients with 'unknown stage' are likely to have stage III-IV disease and do not undergo further diagnostic procedures due to poor prognosis at time of diagnosis. Also, the distribution of 'known' stages was similar between the cancer registries. Second, the seventh instead of the eighth edition of the TNM classification was used in the analyses due to data availability. As showed by external validation studies, the eight edition has more prognostic significance.[39,40] On the other hand, the eight edition was not yet in use during the study period (2012-2016). Third, this study included adjusted analyses for age group nevertheless, residual confounding cannot be ruled out. Due to the low the use of radiotherapy, adjusted analyses were not performed. In the sensitivity analyses, patients who deceased within 90 days after diagnosis or tumor resection were excluded and treatment strategies were re-investigated. In patients who did not undergo tumor resection, also the influence of patients without pathological confirmation was investigated. The sensitivity analyses showed that the original results were robust. Caution has to be taken with drawing of conclusions and indicating causal relations regarding the treatment strategies, since treatment selection bias cannot be ruled out.

To the best of our knowledge, this is the first study on elderly patients with stage I-II pancreatic cancer, in three European cancer registries, that gives insight in real world data of treatment strategies and survival. These outcomes are relevant since the pancreatic cancer population is increasing in age and these patients are underrepresented in clinical trials.[7,41] Future studies should focus on selection criteria for (non)-surgical treatment, so that clinicians can offer uniform and tailored treatment across countries and in (inter-) national randomized trials. In this tailored treatment, quality of life plays an pivotal role and studies like the Dutch Pancreatic Cancer Project (PACAP) will provide valuable data.[42]

In conclusion, treatment and survival of patients ≥70 years with stage I-II pancreatic cancer in the EURECCA Pancreas Consortium showed substantial variations between three European registries. This included the rate of tumor resection, (neo)adjuvant chemotherapy and palliative chemotherapy. The use of radiotherapy was limited. Survival of patients who underwent tumor resection and who did not undergo tumor resection also differed between the cancer registries. The findings of this study suggest that patients aged 70 years and older with stage I-II pancreatic cancer benefit of a higher tumor resection and chemotherapy administration rate.

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SUPPLEMENTARY MATERIAL

Table S1. Description of cancer registries.

	Cancer registry		
	BE	**NL**	**NOR**
Registry	Belgian Cancer Registry	Netherlands Cancer registry	Cancer Registry of Norway
Organisation	Population based	Population based	Population based
Inhabitants (x10^6)	11	17	5
Incidence years in provided dataset	2012-2015	2012-2016	2012-2016
Coverage of data	>98%	>95%	>98%
Sources of data	Pathology laboratories and use of medical claims data	Nationwide automated pathological archive (PALGA), National Registry of Hospital Discharge Diagnoses	Electronic reporting by physicians, reports from pathology laboratories, discharge and outpatient data, death registry
Collection of survival data until	01-07-2018	31-01-2018	31-12-2017
Centralisation of surgery	No	18 hospitals	No

Table S2. Distribution of stages in registries.

		Cancer registry					
		BE[a]		**NL[a]**		**NOR**	
		N	**%**	**N**	**%**	**N**	**%**
Stage/Extent	**IA**	104	2.9	167	2.6	Localised	
	IB	221	6.2	491	7.6	182	8.3
	IIA	231	6.5	564	8.7	Regional	
	IIB	513	14.4	792	12.3	465	21.1
	III	273	7.6	781	12.1	Distant	
	IV	1410	39.5	3392	52.6	1008	45.7
	Unknown	822	23.0	264	4.1	551	25.0

[a]Data from dynamic databases, numbers slightly differ from cohort included in study

Table S3. Multivariable sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, including cancer registry, age group and chemotherapy as factors.

		Overall survival of patients who underwent tumor resection (N=1354)		Overall survival of patients who did not undergo tumor resection (N=1243)	
		HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Cancer registry	**BE**	**Reference**		**Reference**	
	NL	1.10 (0.95-1.27)	0.127	1.29 (1.11-1.49)	0.001
	NOR	0.70 (0.57-0.87)	0.001	1.12 (0.93-1.35)	0.217
Age group	**70-74**	**Reference**		**Reference**	
	75-79	1.19 (1.03-1.38)	0.018	1.16 (0.97-1.39)	0.099
	≥80	1.20 (0.99-1.45)	0.070	1.19 (1.00-1.40)	0.040
(Neo)adjuvant chemotherapy[a]	**No**	**Reference**		-	-
	Yes	0.82 (0.71-0.94)	0.007	-	-
Palliative chemotherapy[b]	**No**	-	-	**Reference**	
	Yes	-	-	1.08 (0.92-1.27)	0.332

HR: hazard ratio; CI: confidence interval
[a]Chemotherapy before or after tumor resection or both
[b]Chemotherapy in patients who did not undergo tumor resection

Table S4. Sensitivity analyses for overall survival, excluding patients who deceased within 90 days after diagnosis or tumor resection, by cancer registry, age group and treatment strategy.

		Total			Cancer registry								
					BE			NL			NOR		
Age group	**Treatment strategy**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**	**N**	**%**	**OS (95%CI)[a]**
Total	**Tumor resection + (neo)adjuvant chemotherapy**	602	23.2	22 (19-25)	271	33.7	21 (17-25)	296	22.2	23 (19-27)	35	7.6	27 (14-40)
	Tumor resection alone	752	28.9	18 (17-20)	173	21.5	19 (15-24)	360	27.0	15 (12-17)	219	47.3	26 (23-28)
	Palliative chemotherapy	293	11.3	9 (8-11)	173	21.5	11 (10-12)	67	5.0	9 (8-11)	53	11.4	9 (8-11)
	No treatment	951	36.6	8 (7-9)	188	23.4	9 (7-11)	607	45.6	8 (8-9)	156	33.7	8 (7-9)
	Total	**2599**	**100**	**13 (12-14)**	**805**	**100**	**15 (13-16)**	**1331**	**100**	**12 (11-12)**	**463**	**100**	**16 (14-19)**
70-74	**Tumor resection + (neo)adjuvant chemotherapy**	366	41.6	24 (20-28)	140	55.1	25 (19-31)	198	44.6	24 (18-29)	28	15.5	27 (9-45)
	Tumor resection alone	266	30.3	22 (18-26)	36	14.2	26 (17-35)	133	30.0	16 (13-19)	97	53.6	34 (23-44)
	Palliative chemotherapy	118	13.4	11 (9-13)	56	22.0	12 (9-14)	36	8.1	11 (8-13)	26	14.4	10 (8-11)
	No treatment	129	14.7	12 (10-13)	22	8.7	9 (5-14)	77	17.3	7 (6-8)	30	16.6	12 (10-13)
	Total	**879**	**100**	**18 (17-20)**	**254**	**100**	**18 (16-21)**	**444**	**100**	**16 (14-18)**	**181**	**100**	**25 (19-32)**
75-79	**Tumor resection + (neo)adjuvant chemotherapy**	200	24.8	20 (18-23)	104	40.5	20 (17-24)	89	21.5	20 (15-26)	7	5.2	27 (12-42)
	Tumor resection alone	298	37.0	16 (14-18)	68	26.5	16 (10-22)	149	36.0	13 (10-16)	81	60.4	22 (17-27)
	Palliative chemotherapy	101	12.5	7 (2-12)	53	20.6	11 (10-13)	30	7.2	9 (7-11)	18	13.4	7 (2-12)
	No treatment	205	25.5	8 (7-9)	32	12.5	12 (10-14)	145	35.0	8 (7-9)	28	20.9	8 (6-9)
	Total	**805**	**100**	**14 (12-15)**	**257**	**100**	**16 (13-19)**	**414**	**100**	**11 (10-13)**	**134**	**100**	**18 (14-21)**
≥80	**Tumor resection + (neo)adjuvant chemotherapy**	36	3.9	21 (13-30)	27	9.2	26 (9-21)	9	1.9	20 (19-21)	0	0.0	-
	Tumor resection alone	188	20.5	17 (15-19)	69	23.5	17 (11-24)	78	16.5	16 (12-19)	41	27.7	20 (11-29)
	Palliative chemotherapy	74	8.1	10 (8-11)	64	21.8	10 (8-12)	1	0.2	4	9	6.1	8 (7-10)
	No treatment	617	67.4	8 (7-9)	134	45.6	8 (7-10)	385	81.4	9 (8-9)	98	66.2	8 (7-9)
	Total	**915**	**100**	**10 (9-10)**	**294**	**100**	**11 (9-12)**	**473**	**100**	**9 (9-10)**	**148**	**100**	**10 (8-12)**

[a]Median overall survival in months after tumor resection (patients who underwent tumor resection) or after diagnosis (patients who did not undergo tumor resection) and 95% confidence interval

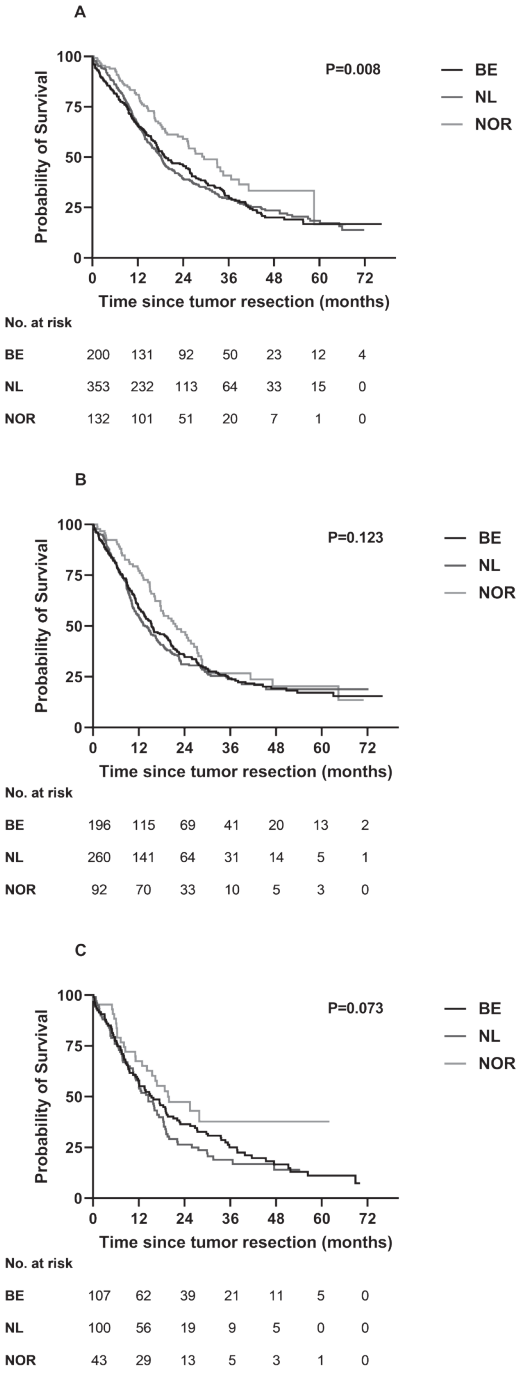

Figure S1 A-C. Overall survival of patients who underwent tumor resection by cancer registry for: (A) age group 70-74 years, (B) age group 75-79 years, (C) age group ≥80 years.

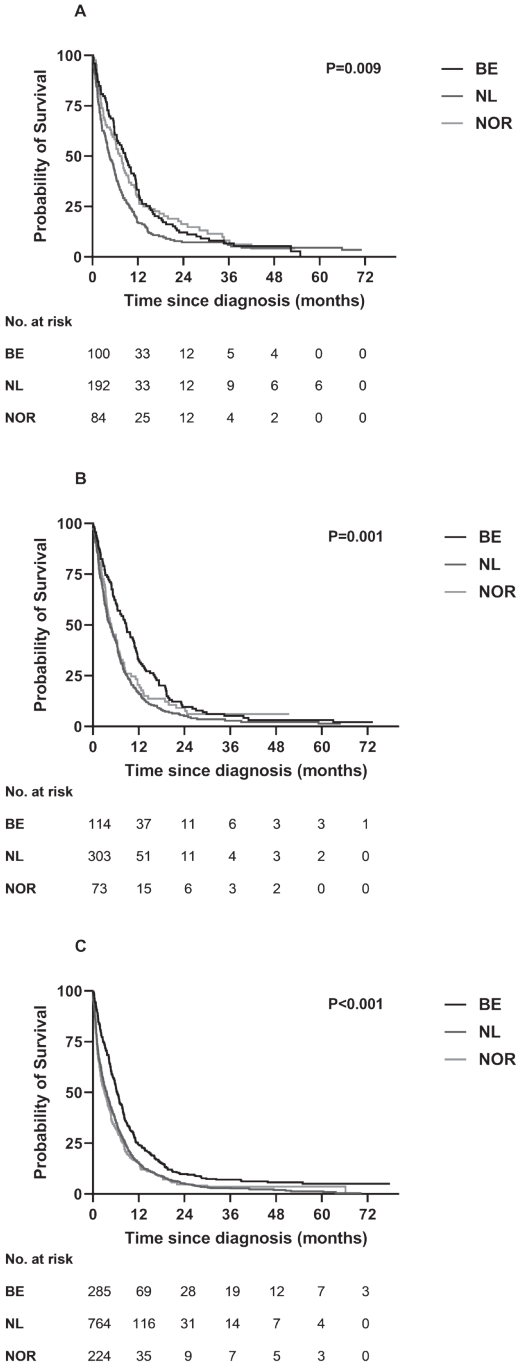

Figure S2 A-C. Overall survival of patients who did not undergo tumor resection by cancer registry for: (A) age group 70-74 years, (B) age group 75-79 years, (C) age group ≥80 years.

ASO Author Reflections: Can Utilization of Cancer Registry Data Contribute to Solving the Lack of Evidence for Older Pancreatic Cancer Patients?

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To The Editor

PAST

Pancreatic cancer has a poor prognosis with a 5-year survival of approximately 7%.[1] Only patients with stage I-II (localized disease) have a chance for long-term survival after resection. Recently, some advances were made in patients with localized disease who were treated with neoadjuvant chemoradiation therapy[2] or adjuvant FOLFIRINOX[3]. Unfortunately, the median age of patients included in these randomized controlled trials (63-67) are not representative for the general pancreatic cancer population.[4] Older patients are often not included in clinical trials, leading to a knowledge gap in treating older patients. The international EURECCA (European Registration of Cancer Care) project is a research committee supported by the European Society of Surgical Oncology. The aim of EURECCA is to utilize cancer registry data to compare and improve treatment strategies.[5]

PRESENT

In this international EURECCA study[6], treatment strategies and survival outcomes of patients 70 years and older with stage I-II pancreatic cancer were compared in the Belgian, Dutch and Norwegian national cancer registries. Large differences were observed in the use of surgery and (neo)adjuvant and palliative chemotherapy. Only 23% of patients received the current standard-of-care (tumor resection preceded or followed by chemotherapy). Even stratified for treatment strategy, overall survival differed significantly between the cancer registries. Although this study provides no insight in quality of life, it appears that adequately selected older patients and more aggressive treatment can result in better overall survival.

FUTURE

Although the quantity and quality of randomized clinical trials is increasing[7], we still expect that elderly patients will often be excluded. Therefore, the utilization of cancer registry data offers a solution in research of elderly patients. Another advantage over randomized clinical trials data, is that cancer registry data is readily available and population-based, thereby minimizing selection bias. EURECCA also aims to create awareness of the large variation in treatment strategies between cancer registries and generate new hypotheses for future research.[5] Future studies are needed to identify selection criteria for local and systemic treatment, so that clinicians can offer tailored treatment to older patients with pancreatic cancer.

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CHAPTER 4

Pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy: a worldwide survey among surgeons

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HPB (Oxford). 2022 Apr;24(4):558-567. doi: 10.1016/j.hpb.2021.09.006. Epub 2021 Sep 24. PMID: 34629261.

ABSTRACT

Background: The aim of this survey was to assess practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy on a global basis.

Methods: This survey study among surgeons from eight (inter)national scientific societies was performed according to the CHERRIES guideline.

Results: Overall, 236 surgeons completed the survey. ERAS protocols are used by 61% of surgeons and respectively 82%, 93%, 57% believed there is a relationship between pain management, fluid therapy, and thromboprophylaxis and clinical outcomes. Epidural analgesia (50%) was most popular followed by intravenous morphine (24%). A restrictive fluid therapy was used by 58% of surgeons. Chemical thromboprophylaxis was used by 88% of surgeons. Variations were observed between continents, most interesting being the choice for analgesic technique (transversus abdominis plane block was popular in North America), restrictive fluid therapy (little use in Asia and Oceania) and duration of chemical thromboprophylaxis (large variation).

Conclusion: The results of this international survey showed that only 61% of surgeons practice ERAS protocols. Although the majority of surgeons presume a relationship between pain management, fluid therapy and thromboprophylaxis and clinical outcomes, variations in practices were observed. Additional studies are needed to further optimize, standardize and implement ERAS protocols after pancreatic surgery.

INTRODUCTION

There is increasing interest in Enhanced Recovery After Surgery (ERAS) protocols as a means of improving clinical outcomes, although to date there is limited data on pancreatoduodenectomy (PD).(1-3) Pain management, fluid therapy and thromboprophylaxis are among key elements in all ERAS protocols and are believed to be equally important following PD. Recent studies have shown an association between low compliance to ERAS protocols and decreased clinical outcomes such as more overall, respiratory, infectious, and major complications (Clavien-Dindo ≥III), longer length of hospital stay and more readmissions following PD.(4, 5)

Although epidural analgesia is recommended over intravenous morphine in the recent ERAS Society guideline for PD(1), the optimal pain management remains controversial, and the reported use of epidural analgesia varies from 11-85%.(6) There are only a few well-conducted randomized controlled pain management trials reporting on patients undergoing PD(7-9) and to date the role of transversus abdominis plane blocks has not been assessed for these patients.

Avoidance of fluid overload and a goal-directed fluid therapy algorithm using intra- and postoperative non-invasive monitoring are recommended in the ERAS Society guidelines for PD.(1) Recent randomized trials on liberal or restrictive fluid therapy have brought conflicting evidence and have not led to a consensus.(10-12) A recent meta-analysis revealed an association between restrictive fluid therapy and lower mortality, although no association with morbidity was observed. It was concluded that more research is needed, ideally by collaboration of surgeons, anaesthesiologists and critical care physicians.(13)

The ERAS Society guidelines for PD recommends mechanical and chemical thromboprophylaxis (low molecular weight or unfractionated heparin) until hospital discharge and extended thromboprophylaxis (four weeks) in patients with cancer.(1) Although many (inter)national thromboprophylaxis guidelines are available, there is still debate about the choice and duration of the appropriate thromboprophylaxis.(14) Despite all guidelines recommend extended thromboprophylaxis in patients with cancer, there is no specific definition.(15)

The aim of this study was to obtain a global assessment of current perioperative practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing PD among surgeons.

METHODS

Study design and participants

This survey study was performed and reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).(16) Institutional Review Board approval was not requested since no patients were involved and informed consent was implied when participants completed the survey.

An online survey (LimeSurvey; https://www.limesurvey.org) was designed in collaboration within an international research team. The survey was tested for usability and technical functionality. An invitation e-mail for the closed-survey (i.e. only accessible through invitation) was sent out from November 2019 through July 2020 to members of six international societies (International Hepato-Pancreato and Biliary Association (HPBA), Americas-HPBA, Asian-Pacific-HPBA, Australia-New Zealand-HPBA, Enhanced Recovery After Surgery Society and American Society for Enhanced Recovery) and two national societies (Association de chirurgie hépato-bilio-pancréatique et transplantation, Society of American Gastrointestinal and Endoscopic Surgeons). The link to the survey also appeared on several social media channels.

In the invitation e-mail, participants were informed about the topic, research team and aim of the survey, the duration (~five minutes) and the fact that all answers were being collected anonymously. Participants received up to three reminders. The survey was closed end of July 2020. The total number of invited participants and response rates was not calculated, since there is overlap between memberships of the international and national associations. IP addresses or cookies were used to prevent multiple responses by the same individual and were deleted after the survey was closed.

Survey

The content of the survey is available at request. The first part of the survey consisted of questions regarding characteristics of the participants, for example: scope of practice, experience, and annual volume. The second part of the survey was focused on pain management: analgesic technique, standardized protocols, availability of an acute pain service, most effective analgesic technique, and the presumed relationship between analgesic technique and clinical outcome. The third part of the survey covered issues concerning fluid therapy: standardized protocols, type of fluid therapy, means of monitoring, and presumed relationship between fluid therapy and clinical outcome. The fourth and final part of the survey examined thromboprophylaxis practices: the use of mechanical and chemical thromboprophylaxis, duration of thromboprophylaxis, indications for thromboprophylaxis, and presumed relationship between thromboprophylaxis and clinical outcome.

Survey questions included multiple-choice and open questions and were not randomized or altered. Adaptive questioning was used based on the answers in the survey. The survey consisted of 8 pages and a total of 41 questions. A completeness check was performed before submission of the survey and participants were given the chance to review and change their answers. No time limit was set for filling in the survey. Responders were given the option to include their information (e-mail address) separately to receive the study results. No other incentives were offered.

Statistical analyses

No weighting of items or propensity score matching was used to adjust for a potential non-representative sample. Participants who did not complete the first part of the survey (characteristics) were excluded. Continuous variables were presented as median with interquartile range (IQR). Categorical variables were presented as numbers (percentages) and compared by means of Chi-square or Fisher's Exact tests. Participants were analysed in total and compared by continent. IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis.

RESULTS

Participants

In total, 272 surgeons responded to the survey during its open window between November 2019 and July 2020 (Table 1). Thirty-six responses were excluded since they did not complete page 2 (first part of the survey on characteristics). Most participants were from Europe (42%), North America (21%) and Asia (19%). The median age of participants was 45 years old (IQR 37-54), the majority were male (86%), were employed at an academic hospital (79%) and the scope of practice was hepato-pancreato-biliary surgery (71%). In 20% there were a dedicated pancreatic surgeon and anaesthesiologist, in 60% there was a dedicated pancreatic surgeon and in 21% there was no dedicated team. ERAS protocols after pancreatic surgery were practiced in 61% of the participants' institutes (Figure 1). The highest rates of practising ERAS protocols were reported in North America (73%) and Asia (72%) (Figure 1). ERAS protocols were practiced by 62% of surgeons employed at an academic and 54% of surgeons employed at a non-academic hospital (P=0.425).

Table 1. Baseline characteristics of participants

	Surgeons	
Question	**N**	**%**
What is your scope of practice?		
HPB	168	71.2
Surgical oncology	28	11.9
Transplant surgery	3	1.3
General surgery	29	12.3
Other	8	3.4
What is your sex?		
Male	203	86.4
Female	32	13.6
Missing	1	
What is your age in years?		
Median (IQR)	45	37-54
Missing	2	
How many years of work experience do you have after your residency?		
Median (IQR)	12	5-22
In which continent do you work?		
North America	49	20.8
South America	15	6.4
Europe	100	42.4
Africa	4	1.7
Asia	45	19.1
Oceania	23	9.7
Are you employed at an academic hospital?		
Yes	161	78.5
No	44	21.5
Missing	31	
How many PDs does your institution perform annually?		
Median (IQR)	35	20-60
How many PDs do you perform annually?		
Median (IQR)	15	7-29
Missing	40	
Is there a dedicated team for pancreatic surgery?		
Yes, both a pancreatic surgeon and anaesthesiologists	40	19.5
Yes, a pancreatic surgeon	122	59.5
No, there is no dedicated team	42	20.5
Other	1	0.5
Missing	31	

Abbreviations: HPB: hepatopancreatobiliary; IQR: interquartile range; PD: pancreatoduodenectomy

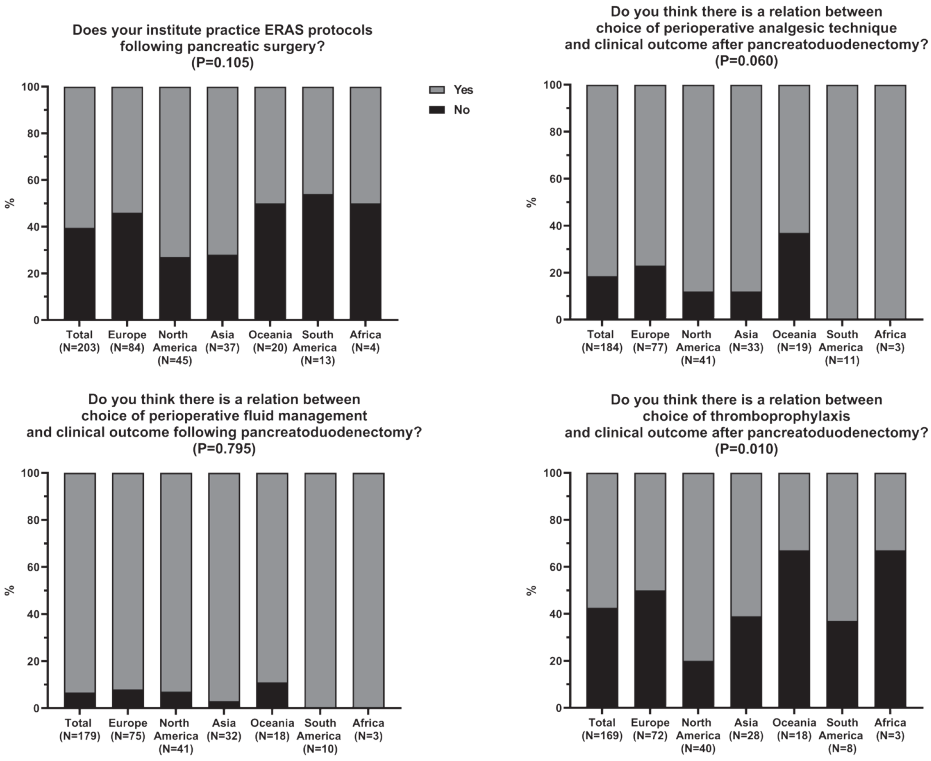

Figure 1. Practice of ERAS protocols following pancreatic surgery and the presumed relationship between perioperative analgesic technique, fluid therapy, thromboprophylaxis, and clinical outcome after PD

Pain management

Overall, the most frequently used analgesic technique for an open PD was epidural analgesia (50%), followed by intravenous morphine (24%), spinal analgesia (10%), transversus abdominis plane block (9%), and continuous wound infiltration (8%) (Figure 2).

In 36% of responses, the surgical staff was responsible for postoperative pain management, in 34% the anaesthesiology staff, and in 26% a dedicated acute pain service team (Table 2). Initial analgesia was stopped before or on postoperative day 3 in 75% of patients and in 25% on postoperative day 4 or later. After discontinuation of the initial analgesic technique, a standardized protocol was used by 65% of participants. In case of minimally invasive (laparoscopic or robot assisted) PD, 51% of participants used a different analgesia technique (Figure 3). An association between the choice of perioperative analgesia technique and clinical outcome after PD was assumed by 82% of participants (Figure 1).

Epidural analgesia and intravenous morphine were the most frequently used analgesic technique in all continents, except for North America, where the transversus abdominis plane block was almost equally popular (Figure 2). The responsibility for postoperative pain management was more clearly distributed in North America, 61% of participants reported that the surgical staff was responsible, and in Oceania, 79% reported that the dedicated acute pain service was responsible (Table S1). The assumed relationship between choice of analgesia technique and clinical outcome varied between the continents; with 88% assuming a relationship in Asia and North America and 63% in Oceania (Table S1).

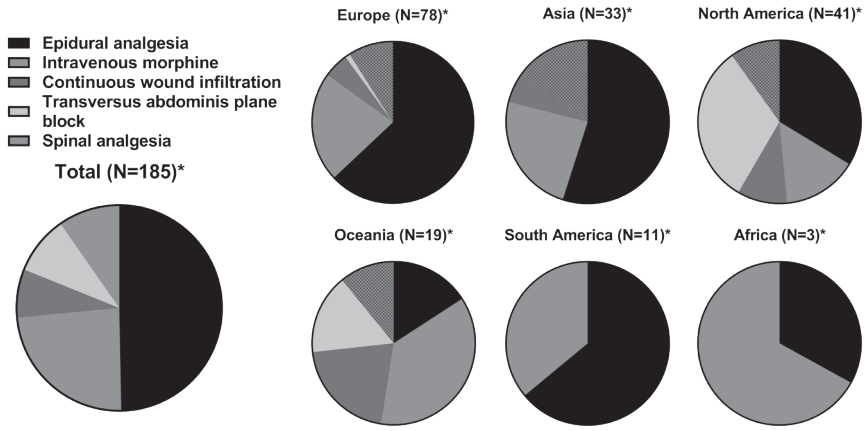

Figure 2. Most popular perioperative analgesic technique in patients undergoing PD

Fluid therapy

A standardized protocol for fluid management was used by 54% of participants for an open PD and 58% reported the use of restrictive fluid therapy in the protocol (Table 2). In case of a minimally invasive procedure 30% of participants used a different protocol (Figure 3). The first night after surgery 94% of participants reported that patients were admitted to a monitored environment. An association between the choice of perioperative fluid management and clinical outcome after PD was assumed by 93% of participants (Figure 1).

In contrast to the other continents, a minority of participants in Asia (44%) and Oceania (39%) reported the use of restrictive fluid therapy (Table S1). Little variation in the assumed relationship between choice of fluid management and clinical outcome was reported between continents (89-100%) (Figure 1).

Table 2. Perioperative pain management and fluid therapy in patients undergoing PD

	Surgeons	
Question	**N**	**%**
Perioperative pain management		
Who manages the postoperative pain and initial analgesic technique (e.g. epidural analgesia, intravenous analgesia with opioids) when the patient is on the ward?		
Surgical staff	67	36.2
Anaesthesiology staff	63	34.1
Dedicated Acute Pain Service team	48	25.9
Other	7	3.8
Missing	51	
Which method, regardless of analgesic technique, is the most effective following open PD in your opinion (taking into account analgesia, side effects and patient satisfaction)?		
Patient controlled	122	66.3
Continuous	62	33.7
Missing	52	
Is there a set postoperative day for discontinuation of the initial analgesic technique following open PD?		
Yes	91	49.5
No	93	50.5
Missing	52	
Which day is set as postoperative day for discontinuation of the initial analgesic technique following open PD?		
POD 0	2	2.2
POD 1	3	3.3
POD 2	23	25.3
POD 3	40	44.0
POD 4	13	14.3
POD ≥5	10	11.0
Missing	145	
Is there a standardized protocol for pain management after discontinuation of the initial analgesic technique?		
Yes	120	65.2
No	64	34.8
Missing	52	
Is the standardized protocol for pain management after discontinuation of the initial analgesic technique an oral multimodal protocol?		
Yes	100	83.3
No	20	16.7

Table 2. Continued

Perioperative fluid therapy		
Does your institution have a standardized protocol for fluid management during open PD?		
Yes	96	53.6
No	83	46.4
Missing	57	
Does the protocol at your institution describe the use of restrictive fluid therapy (near zero fluid balance) during and following open PD?		
Yes	103	57.5
No	76	42.5
Missing	57	
Do you replace fluid volume according to output of drainage tubes (enteral tube, abdominal drains, biliary/pancreatic drains) following PD?		
Yes	102	57.3
No	76	42.7
Missing	58	
What is the planned destination for patients during the first night following open pancreatoduodenectomy?		
Monitored environment (intensive or medium care unit, post anaesthesia care unit)	137	76.5
Monitored on ward	30	16.8
Unmonitored on ward	12	6.7
Missing	57	

Abbreviations: POD: postoperative day; PD: pancreatoduodenectomy

Thromboprophylaxis

The use of mechanical thromboprophylaxis was reported by 90% of participants (Table 3). The most used mechanical prophylaxis following open PD were early mobilization (77%), TED stockings (66%) and calf compression (61%). The use of chemical thromboprophylaxis was reported by 88% of participants following open PD. Most participants stopped the chemical prophylaxis on discharge (27%) or four weeks after surgery (52%) (Figure 4).

Different thromboprophylaxis protocols were used in 23% for a benign indication and in 7% for a minimally invasive PD (Table 3, Figure 3). Different thromboprophylaxis protocols were also used in 40% in case of an arterial resection and 23% in case of a venous resection (Figure 4). Most participants added a platelet inhibitor for an arterial (68%) or a venous (47%) resection. An association between the choice of thromboprophylaxis and clinical outcome after PD was assumed by 57% of participants (Figure 1).

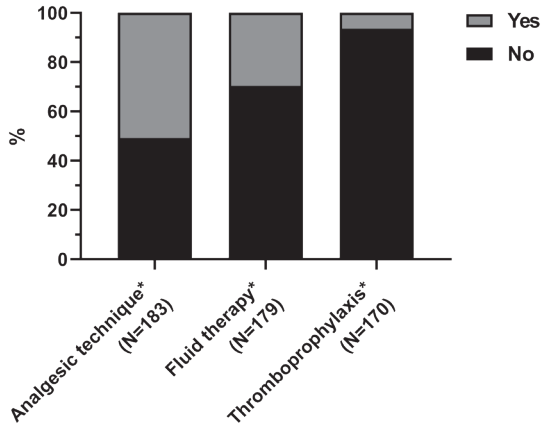

Figure 3. Use of a different protocol of perioperative analgesic technique, fluid therapy, and thromboprophylaxis in minimally invasive compared to open PD

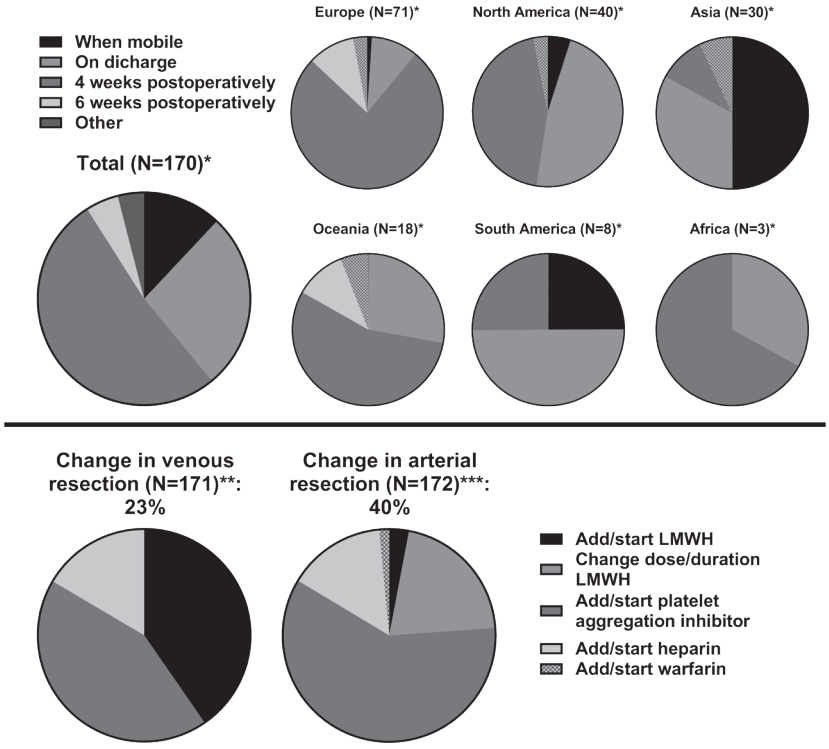

Figure 4. Duration of thromboprophylaxis in open PD and change in protocol in case of venous and arterial resection

In comparison to other continents, participants from Asia reported limited use of chemical thromboprophylaxis (48%) in their protocols (Table S1). The majority in Asia preferred to stop chemical thromboprophylaxis when the patient was mobile (50%), in North America at discharge (48%) and in Europe and Oceania at four weeks postoperatively (76% and 56%) (Figure 4). For an arterial or venous resection, in Oceania a different protocol was used in 11% and 0%, in contrast to 48% and 40% in North America and 55% and 23% in Asia (Table S1). The assumed relationship between choice of prophylaxis and clinical outcome varied between the continents; with 80% in North America assuming a relationship and only 33% in Oceania (Figure 1).

Table 3. Thromboprophylaxis in patients undergoing PD

	Surgeons	
Question	**N**	**%**
Does the protocol at your institution describe the use of mechanical thromboprophylaxis?		
Yes	155	90.1
No	17	9.9
Missing	64	
Which methods of mechanical thromboprophylaxis are used following open PD? *		
TED stockings	102	65.8
Calf compressors	95	61.3
Foot-pump	27	17.4
Early mobilization	120	77.4
Other	1	0.6
Does the protocol describe the use chemical thromboprophylaxis following open PD?		
Yes	151	87.8
No	21	12.2
Missing	64	
Would you use a different protocol of thromboprophylaxis if this was a patient with a benign indication for PD?		
Yes	38	22.5
No	131	77.5
Missing	67	

Abbreviations: TED: Thrombo-embolic deterrent; LMWH: low-molecular weight heparin; PD: pancreatoduodenectomy
*Multiple answers possible

DISCUSSION

This international survey of 236 surgeons gives insight into the current global perioperative practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing PD. This survey demonstrates tremendous variation in perioperative practice by pancreatic surgeons around the world. Furthermore, there is limited compliance to the current ERAS Society guideline for PD(1) regarding pain management, fluid therapy and thromboprophylaxis and only 61% of surgeons practice ERAS protocols. Most surgeons assume a relationship between pain management, fluid therapy and thromboprophylaxis and clinical outcome following PD, respectively 82%, 93% and 57%. The preferred method for analgesia was epidural analgesia (50%), followed by intravenous morphine (25%). Restrictive fluid therapy is practiced by 58% of surgeons. Mechanical and chemical thromboprophylaxis are frequently used after PD (90% and 88%), however the duration of chemical prophylaxis varies. In case of minimally invasive surgery most surgeons only changed the analgesia technique (51%), but did not amend fluid therapy (30%) or thromboprophylaxis (7%). Variations between continents exist, mainly related to the choice of analgesia technique, use of restrictive fluid therapy, and duration of chemical thromboprophylaxis.

Postoperative pain management is one of the most important pillars of ERAS strategies as adequate pain management leads to shorter hospital stay and less postoperative complications.(17) Epidural analgesia is the most used analgesic technique, in line with the current ERAS Society guideline for PD which strongly recommends epidural analgesia and a multimodal opioid sparing strategy.(1) A previous meta-analysis of non-randomized studies showed a marginal difference with a questionable clinical relevance in mean pain scores between epidural analgesia and intravenous morphine, yet did confirm a reduction in complications, length of stay and mortality in patients receiving epidural analgesia.(6) However, a recent randomized study observed conflicting results with similar gastrointestinal morbidity for both analgesic techniques.(9) The ERAS Society guideline for PD also states the use of continuous wound infiltration as a reasonable alternative to epidural analgesia.(1) In spite of this recommendation, the use of continuous wound infiltration was rarely reported in the survey. Interestingly, in North America the transversus abdominis plane block was highly ranked as the most commonly used technique for analgesia, although this preference was not reported on other continents. This is probably due to personal preferences and experience, since no research has been done on the effectiveness of this analgesic technique in PD. Although it has been shown to be beneficial following other upper gastrointestinal resections including hepatectomy and gastrectomy.(18, 19) In the survey, 66% of surgeons preferred patient controlled analgesia over continuous infusion. Despite evidence of improved effectiveness and higher patient satisfaction within other fields of surgery(20), few studies have investigated this in

pancreatic surgery.(6) More research is needed to determine the optimal analgesic technique for open PD and separately for minimally invasive procedures. Half of the surgeons reported the use of a different analgesic technique in minimally invasive PD, without studies being available which investigated this.

The importance of fluid therapy is affirmed by the high assumed association with clinical outcome (93%). However, the optimal protocol for fluid management is still under debate, due to the use of varying definitions (liberal, restrictive, zero-balance fluid therapy) and low compliance rates.(5, 10-12) This is confirmed in the survey by the large variation in clinical practices. The current ERAS Society guideline for PD strongly recommends avoiding fluid overload to improve outcomes. Despite this recommendation, only 58% of surgeons report the use of restrictive fluid therapy in their institutional protocol. Interestingly, Asia and Oceania reported relatively little use of restrictive fluid therapy and yet do largely assume an association with clinical outcome. A randomized trial in the context of an ERAS protocol found that intraoperative goal directed fluid therapy reduced administration of (intraoperative) fluids, shortened the length of hospital stay and reduced postoperative complications in patients undergoing PD.(21) Additional research is needed to confirm these results and optimize the goal directed fluid therapy protocols, also for minimally invasive procedures.

Thromboprophylaxis protocols are considered one of the highest levels of evidence available in ERAS Society guideline for PD.(1) The recommendation to use extended chemical prophylaxis of four weeks for cancer is only practiced by 52% of surgeons. Especially in Asia and North America, prophylaxis is often discontinued when a patient is mobile or discharged. This poor adherence to the ERAS Society guideline for PD might be explained by differences in health care systems or cultural objections to self-injection of chemical thromboprophylaxis. Few surgeons used a different protocol for a benign indication, possibly exposing these patients to an unnecessary higher risk of four weeks of prophylaxis. In a previous study, we investigated three different thromboprophylaxis regimens and concluded that a high dose of nadroparin (5700IU once daily) for six weeks is associated with an increased risk of post-pancreatectomy haemorrhage. The benefits of (extended) thromboprophylaxis should be carefully reconsidered in case of risk factors for post-pancreatectomy haemorrhage such as postoperative pancreatic fistula.(22) The use of mechanical prophylaxis was widespread in our survey with a weak recommendation in the guideline as an additional measure. However, the compliance to early mobilization has been shown to be difficult, possibly due to the frequent use of epidural analgesia.(5) Standard use of physiotherapists could help stimulate a higher compliance rate. It is questionable if there is enough support to further investigate the optimal thromboprophylaxis protocol due to a relatively low assumed association with clinical outcome (53%). Patients with vascular resections are at high risk of thrombosis.

(23) Our survey showed that 40% and 23% used a different protocol for arterial and venous resections and there were large variations in type, dose and duration of the thromboprophylaxis protocols. This could create possibilities for optimizing the thromboprophylaxis in these high-risk patients.

This survey does have some limitations. Firstly, the sample is rather small and heterogeneous (for example the distribution among the different continents). Furthermore, the exact the number of invited participants and the response rate remain unknown. Secondly, the relatively high representation of academic surgeons that could be explained by potential selection bias due to the participation of several (inter)national scientific societies. However, since PD is increasingly being centralized to high-volume centres, the sample could equally be considered representative. Lastly, responses are preferences and perceptions of individuals (response bias) were not confirmed by patient-data.

Overall, the observed variations in perioperative practice have to be considered during interpretation and extrapolation of study results to other hospitals or regions. This study also highlights the issue of surgeons not practicing evidence-based medicine. The exact reasons for the choice of specific perioperative practices were not surveyed in this study. Another survey study among surgeons showed that the most common reasons for not implementing recommended practices are: scepticism regarding the validity of the applied methodology of the available evidence, low clinical relevance and organizational or financial considerations. Clinically relevant and well-designed randomized trials with adequate methodology and external validity and global dissemination of the results (besides conventional methods, visual abstracts and videos have a high potential) are needed to increase the compliance to recommended practices.(24) This will create more uniformity of protocols over the globe and further optimize the perioperative care after PD.

In conclusion, this international survey showed that there is a limited compliance to the current ERAS Society guidelines for PD and only 61% of surgeons practice to ERAS protocols. Although the majority of surgeons presume a relationship between pain management, fluid therapy, thromboprophylaxis, and clinical outcomes, large variations in practices were observed. Additional studies are needed to further optimize, standardize, and implement ERAS protocols after pancreatic surgery into daily practice.

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SUPPLEMENTARY MATERIAL

Table S1. Subgroup analysis by continent

	Europe		North America		Asia		Oceania		South America		Africa		
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**P-value**
	100	42.4	49	20.8	45	19.1	23	9.7	15	6.4	4	1.7	
Baseline													
What is your scope of practice?													0.008
HPB	72	72.0	29	59.2	34	75.6	21	91.3	11	73.3	1	25.0	
Surgical oncology	12	12.0	11	22.4	3	6.7	0	0.0	1	6.7	1	25.0	
Transplant surgery	0	0.0	0	0.0	3	6.7	0	0.0	0	0.0	0	0.0	
General surgery	15	15.0	7	14.3	2	4.4	1	4.3	2	13.3	2	50.0	
Other	1	1.0	2	4.1	3	6.7	1	4.3	1	6.7	0	0.0	
Does your institute practice ERAS protocols following pancreatic surgery?													0.105
Yes	45	53.6	33	73.3	28	71.8	10	50.0	6	46.2	2	50.0	
No	39	46.4	12	26.7	11	28.2	10	50.0	7	53.8	2	50.0	
Missing	16		4		6		3		2		0		
Pain management													
Who manages the postoperative pain and initial analgesic technique (e.g. epidural analgesia, intravenous analgesia with opioids) when the patient is on the ward?													<0.001
Surgical staff	22	28.2	25	61.0	15	45.5	1	5.3	3	27.3	1	33.3	
Anaesthesiology staff	32	41.0	9	22.0	11	33.3	3	15.8	6	54.5	2	33.3	
Dedicated acute pain service team	20	25.6	5	12.2	7	21.2	15	78.9	1	9.1	0	0.0	
Other	4	5.1	2	4.9	0	0.0	0	0.0	1	9.1	0	0.0	
Missing	22		8		12		4		4		1		

Table S1. Continued

Organize the analgesia techniques by descending frequency of use following open PD:													
Rank 1: EA / ivM / CWI / TAP / spinal	62.8 / 21.8 / 5.1 / 1.3 / 9.0		34.1 / 14.6 / 9.8 / 31.7 / 9.8		54.5 / 24.4 / 6.1 / 0.0 / 15.2		15.8 / 36.8 / 21.1 / 15.8 / 10.5		63.6 / 36.4 / 0.0 / 0.0 / 0.0		33.3 /66.6 / 0.0 / 0.0 / 0.0		<0.001
Missing	22		8		12		4		4		1		
Rank 2: EA / ivM / CWI / TAP / spinal	14.1 / 47.4 / 19.2 / 11.5 / 5.1		12.2 / 51.2 / 4.9 / 29.3 / 2.4		24.2 / 42.4 / 18.2 / 12.1 / 3.0		31.6 / 15.8 / 15.8 / 10.5 / 26.3		0.0 / 18.2 / 27.3 / 9.1 / 45.5		66.6 / 0.0 / 0.0/ 33.3 / 0.0		<0.001
Missing	22		8		12		4		4		1		
Which method, regardless of analgesic technique, is the most effective following open PD in your opinion (taking into account analgesia, side effects, and patient satisfaction)?													0.547
Patient controlled	55	71.4	27	65.9	21	63.6	12	63.2	7	63.6	0	0.0	
Continuous	22	28.6	14	34.1	12	36.4	7	36.8	4	36.4	3	100.0	
Missing	23		8		12		4		4		1		
Do you think there is a relation between choice of perioperative analgesic technique and clinical outcome after PD?													0.060
Yes	59	76.6	36	87.8	29	87.9	12	63.2	11	100.0	3	100.0	
No	18	23.4	5	12.2	4	12.1	7	36.8	0	0.0	0	0.0	
Missing	23		8		12		4		4		1		
Fluid therapy													
Does your institution have a standardized protocol for fluid management during open PD?													0.804
Yes	40	53.3	24	58.5	18	56.3	7	38.9	5	50.0	2	66.7	
No	35	46.7	17	41.5	14	43.8	11	61.1	5	50.0	1	33.3	
Missing	25		8		13		5		5		1		
Does the protocol at your institution describe the use of restrictive fluid therapy (near zero fluid balance) during and following open PD?													0.161
Yes	45	60.0	28	68.3	14	43.8	7	38.9	7	70.0	2	66.7	
No	30	40.0	13	31.7	18	56.3	11	61.1	3	30.0	1	33.3	
Missing	25		8		13		5		5		1		

Table S1. Continued

Do you think there is a relation between choice of perioperative fluid management and clinical outcome following PD?												0.795
Yes	69	92.0	38	92.7	31	96.9	16	88.9	10	100.0	3	100.0	
No	6	8.0	3	7.3	1	3.1	2	11.1	0	0.0	0	0.0	
Missing	25		8		13		5		5		1		
Thromboprophylaxis												
Does the protocol at your institution describe the use of mechanical thromboprophylaxis?												0.651
Yes	64	88.9	37	92.5	26	83.9	17	94.4	8	100.0	3	100.0	
No	8	11.1	3	7.5	5	16.1	1	5.6	0	0.0	0	0.0	
Missing	28		9		14		5		7		1		
Does the protocol describe the use chemical thromboprophylaxis following open PD?												<0.001
Yes	70	97.2	38	95	15	48.4	17	94.4	8	100.0	3	100.0	
No	2	2.8	2	5	16	51.6	1	5.6	0	0.0	0	0.0	
Missing	28		9		14		5		7		1		
At which time the chemical thromboprophylaxis is discontinued following open PD?												<0.001
When mobile	1	1.4	2	5.0	15	50.0	0	0.0	2	25.0	0	0.0	
On discharged	7	9.9	19	47.5	10	33.3	5	27.8	4	50.0	1	33.3	
4 weeks postoperatively	54	76.1	18	45.0	3	10.0	10	55.6	2	25.0	2	66.6	
6 weeks postoperatively	7	9.9	0	0.0	0	0.0	2	11.1	0	0.0	0	0.0	
Other	2	2.8	1	2.5	2	6.7	1	5.6	0	0.0	0	0.0	
Missing	29		9		15		5		7		1		

Table S1. Continued

Would you use a different protocol of thromboprophylaxis in case of an arterial resection?												0.012
Yes	25	34.7	19	47.5	17	54.8	2	11.1	5	62.5	0	0.0	
No	47	65.3	21	52.5	14	45.2	16	88.9	3	37.5	3	100.0	
Missing	28		9		14		5		7		1		
Would you use a different protocol of thromboprophylaxis in case of a venous resection?												0.025
Yes	15	20.8	16	40.0	7	23.3	0	0.0	2	25.0	0	0.0	
No	57	79.2	24	60.0	23	76.7	18	100.0	6	75.0	3	100.0	
Missing	28		9		15		5		7		1		
Do you think there is a relation between choice of thromboprophylaxis and clinical outcome after PD?												0.010
Yes	36	50.00	32	80.0	17	60.7	6	33.3	5	62.5	1	33.3	
No	36	50.00	8	20.0	11	39.3	12	66.7	3	37.5	2	66.7	
Missing	28		9		17		5		7		1		

Abbreviations: HPB: hepatopancreatobiliary; ERAS: enhanced recovery after surgery; PD: pancreatoduodenectomy; EA: epidural analgesia; ivM: intravenous morphine; CWI: continuous wound infiltration; TAP: transversus abdominis plane block

PART II

SURGICAL AND ONCOLOGICAL ASPECTS OF VENOUS RESECTIONS IN PANCREATIC SURGERY

CHAPTER 5

Surgical management and pathological assessment of pancreatoduodenectomy with venous resection: an international survey among surgeons and pathologists

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ABSTRACT

Background: The aim of this survey was to gain insights in the current surgical management and pathological assessment of pancreatoduodenectomy with portal-superior mesenteric vein resection (VR).

Methods: A systematic literature search was performed to identify international expert surgeons (N=150) and pathologists (N=40) who published relevant studies between 2009-2019. These experts and Dutch surgeons (N=17) and pathologists (N=20) were approached to complete an online survey.

Results: Overall, 76 (46%) surgeons and 37 (62%) pathologists completed the survey. Most surgeons (71%) estimated that preoperative imaging corresponded correctly with intraoperative findings of venous involvement in 50-75% of patients. An increased complication risk following VR was expected by 55% of surgeons, mainly after Type 4 (segmental resection-venous conduit anastomosis). Most surgeons (61%) preferred Type 3 (segmental resection-primary anastomosis). Most surgeons (75%) always perform the VR themselves. Standard postoperative imaging for patency control was performed by 54% of surgeons and 39% adjusted thromboprophylaxis following VR. Most pathologists (76%) always assessed tumor infiltration in the resected vein and only 54% of pathologists always assess the resection margins of the vein itself. Variation in assessment of tumor infiltration depth was observed.

Discussion: This international survey showed variation in the surgical management and pathological assessment of pancreatoduodenectomy with venous involvement. This highlights the lack of evidence and emphasizes the need for research on imaging modalities to improve patient selection for VR, surgical techniques, postoperative management and standardization of the pathological assessment.

INTRODUCTION

Pancreatic cancer infiltration in the portal or superior mesenteric vein (PV-SMV) is not considered a contra-indication for a resection as stated by the International Study Group of Pancreatic Surgery (ISGPS) in 2014.(1) The assessment of venous involvement is important in surgical decision making since the resection margin on the level of the PV-SMV is among the most frequently affected.(2, 3) In selected patients, it is possible to perform a venous resection (VR) to acquire a tumor-free resection margin on the level of the PV-SMV.(1) There is considerable variation in contemporary literature on the clinical management of pancreatoduodenectomy with venous involvement.

The reported correspondence between preoperative imaging, findings during surgery and pathological assessment shows much variation and it remains challenging to select the right patients eligible for VR.(4-6) Despite criteria for assessment of vascular involvement on computed tomography exist(7), absence of tumor infiltration in the resected vein in the final pathology is reported in 39% (range 17–78) of VR.(8) The surgeon has to rely on preoperative imaging, visual inspection, palpation and intraoperative frozen sections in order to distinguish tumor from normal tissue, peritumoral inflammation and fibrosis. This is especially challenging after neoadjuvant chemo -and radiotherapy.(9-11) Routine VR and a "no-touch" technique, without breaching the "capsule" of the tumor at the venous margin, have been described earlier.(12, 13) Some studies reported promising results of intraoperative ultrasound.(14-17) The direct contact with the operative field and real-time imaging provides feedback about the tumor and vascular involvement. Still, it is unknown how often intraoperative ultrasound is used in daily practice and what the added value is in terms of clinically relevant outcome.

The preferred technique for VR is still under debate, illustrated by the variations in applied techniques for VR (e.g. wedge or segmental resection) and reconstruction (e.g. direct closure, end-to-end anastomosis or interposition graft).(18-21) A meta-analysis of 27 studies on pancreatectomy with or without VR showed increased postoperative morbidity, mortality and worse survival after VR, although there was considerable heterogeneity between the included studies.(8) Early PV-SMV thrombosis is a notorious complication which occurs in approximately 6% of patients after VR. Currently, guidelines regarding thromboprophylaxis are lacking.(22)

The relevance of tumor infiltration in the resected vein and depth of tumor infiltration remain unclear. Some studies report an association with decreased survival(4, 23) whereas other studies report no association with survival at all.(5, 21, 24) There are differences between the currently used techniques for macroscopic assessment of the pancreatoduodenectomy specimen by pathologists.(25) It should be noted that none of

the regular used grossing protocols have a detailed description on how to assess and to approach the resected vein. Some studies described the assessment of the resected vein, including the insertion of a plastic probe into the vein in the fresh specimen.(26, 27) Nevertheless, variations in assessment of tumor infiltration, depth of tumor infiltration and resection margins of the resected vein likely exist and hamper generalization of study results.(28, 29)

The aim of this survey was to gain insights in the current surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement by international and Dutch surgeons and pathologists. Furthermore, it aims to identify areas in need for further research to improve the multidisciplinary management of pancreatic cancer with suspected venous involvement.

METHODS

Study design and population

This study was performed and reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).(30) An online surgeon-specific and pathologist-specific survey was designed by the authors. The survey was tested multiple times to guarantee that questions were clearly formulated and unambiguous.

A systematic search was performed to identify international expert surgeons who published relevant studies between January 2009 and June 2019. The email addresses of corresponding authors (surgeons) were identified. These international expert surgeons were approached to complete the online surgeon-specific survey. Furthermore, the corresponding authors were requested to suggest an expert pathologist in their institution. These international expert pancreatic pathologists were approached to complete the online pathologist-specific survey. From every Dutch hospital performing pancreatic surgery (Dutch Pancreatic Cancer Group (DPCG)) at least one representing surgeon and pathologists was approached to complete the survey.

The open and voluntary surveys were sent out via Google Forms (https://docs.google.com/forms). Non-respondents were contacted by e-mail or telephone up to three times. Institutional Review Board approval was not requested since no patients were involved. Informed consent of respondents was implied when the survey was completed.

Survey

The content of the survey is available at request. Survey questions included multiple-choice, checkbox and open questions and were not randomized, altered, or adaptive. Some questions were mandatory. Respondents were able to review and change their answers at the end of the survey. Cookies or IP addresses were not used to prevent multiple entries from the same individual. The request for single entry was stated in the welcome message. Data was collected anonymously and no incentives were offered.

The surgeon-specific survey consisted of 33 questions divided over 12 pages. The survey consisted of questions regarding: surgeon characteristics, volume of VR, correspondence between imaging, surgery and pathology, technical aspects, complications and postoperative care.

The pathologist-specific survey consisted 18 questions divided over seven pages. The survey consisted of questions regarding: volume of VR, assessment of (depth of) tumor infiltration in the resected vein and resection margins of the resected vein.

Definitions

Throughout the manuscript, 'VR' refers to a resection of the PV-SMV, 'venous involvement' refers to (suspected) involvement of the PV-SMV and 'resected vein' refers to the resected PV-SMV itself. Correspondence between preoperative imaging, intraoperative findings and pathological assessment was considered in cases such as: suspected venous involvement on preoperative imaging was also observed during surgery and VR was performed or; VR was performed with tumor infiltration in the resected vein in final pathology. Type of VR was classified according to the ISGPS guidelines: Type 1= partial venous excision with direct closure (venorraphy) by suture closure; Type 2= partial venous excision using a patch; Type 3= segmental resection with primary venovenous anastomosis; Type 4=segmental resection with interposed venous conduit and at least two anastomoses.(1) Extent of sampling of the resected vein for pathological assessment was categorized as 'none' (no assessment), 'most suspected' (assessment of one slice of the resected vein most suspect of tumor infiltration or irradical margin) and 'complete' (assessment of multiple slices of the resected vein).

Statistical analysis

For statistical analysis Statistical Package for the Social Sciences for Windows (version 23.0, SPSS, Inc) was used. All completed surveys were analyzed. No formal sample size calculation was performed. The results are reported for the total cohort and compared by international experts *versus* DPCG surgeons and pathologists. Categorical data were reported as numbers (percentages) and compared by chi-square or Fisher's exact tests. P-values <0.05 were considered significant.

RESULTS

Respondents

Rate of response and estimated percentage of venous resections

In total, 76 of 167 (46%) surgeons and 37 of 60 (62%) pathologists completed the survey (Figure 1). Thirty-seven (49%) surgeons estimated that a VR was performed in 11-20% of patients (Table 1). Fifteen (41%) pathologists estimated that a VR was performed in 5-10% of patients (Table 2).

Surgeon-specific survey

Correspondence between preoperative imaging, surgery and pathology

Correspondence on venous involvement between preoperative imaging and intraoperative findings in 50-75% of patients was estimated by 54 (71%) surgeons. More variation in the estimated correspondence between preoperative imaging or intraoperative findings and pathological assessment was observed (Fig. 2). Intraoperative ultrasound was used by 33 (43%) surgeons (Table 1).

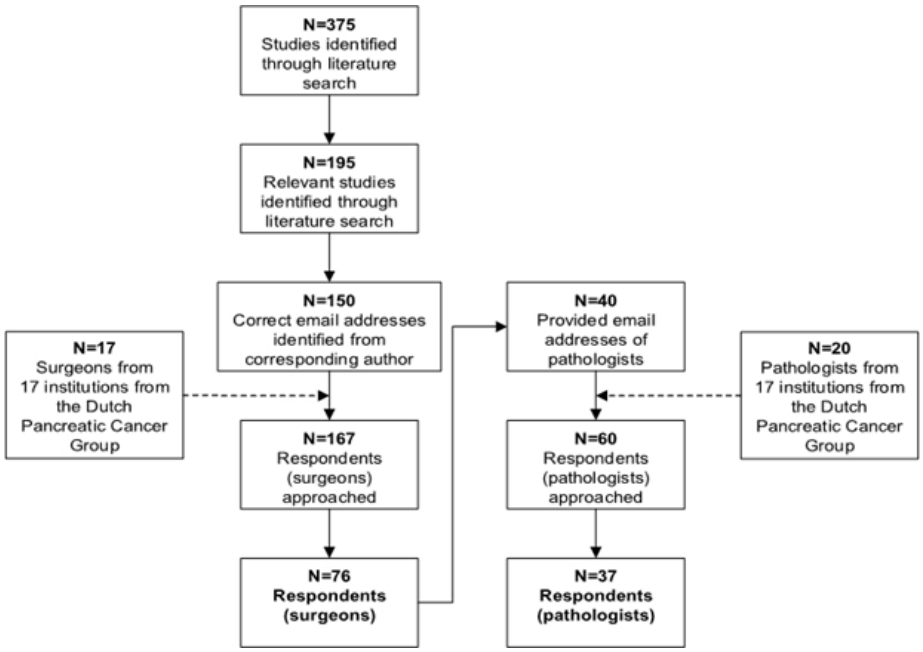

Figure 1. Flow chart of approached surgeons and pathologists.

Table 1. Clinical management of pancreatoduodenectomy with venous involvement by surgeons.

	Total cohort of surgeons	
	N	**%**
Total	**76**	
Continent		
Europe	51	67
America	13	17
Asia/Oceanie	12	16
Estimated percentage of venous resection?		
≥10%	19	25
11-20%	37	49
21-40%	17	22
>40%	3	4
Do you use per-operative imaging (ultrasound)?		
Never	43	57
Selected cases	25	33
Always	8	11
Increased risk of complications?		
Venous resection		
No	34	45
Yes	42	55
Confluens/SMV versus the PV?		
No	21	28
Yes	55	72
Estimated incidence of:		
Post-operative PV-SMV thrombosis?*		
<5%	32	42
5-10%	32	42
>10%	12	16
Post-operative portal hypertension at long-term?		
<5%	42	55
5-10%	20	26
>10%	14	18
Post-operative bleeding of vascular reconstruction?*		
<5%	72	95
5-10%	3	4
>10%	1	1
Post-operative complications due to congestion?*		
<5%	56	74
5-10%	13	17
>10%	7	9

**<90 days after surgery*

Table 2. Assessment of pancreatoduodenectomy specimen with venous involvement by pathologists.

	Total cohort of pathologists	
	N	**%**
Total	**37**	**100**
Continent		
Europe	29	78
America	2	5
Asia/Oceanie	5	14
Unknown	1	3
Estimated percentage of venous resection?		
<5%	10	27
5-10%	15	41
11-20%	3	8
>20%	9	24
Do you assess tumor infiltration in the resected vein?		
Never	3	8
Rarely	1	3
Most often	5	14
Always	28	76
Extent of assessment of tumor infiltration in the resected vein		
None	3	8
Most suspected (part of resected vein)	18	49
Complete (entire resected vein)	15	41
Not standardized	1	3
Do you assess depth of tumor infiltration in the resected vein?		
Never	10	27
Rarely	6	16
Most often	9	24
Always	12	32
Extent of assessment of depth of tumor infiltration in the resected vein?		
None	10	27
Most suspected (part of resected vein)	13	35
Complete (entire resected vein)	14	38
Do you assess the resection margins of the resected vein?		
Never	6	16
Rarely	4	11
Most often	7	19
Always	20	54

Table 2. Continued

Extent of assessment of the resection margins of the resected vein?		
None	6	16
Most suspected (resection margins of the resected vein)	12	32
Complete (all resection margins of the resected vein)	19	51
Do you use additional stainings for assessment of the resected vein?		
No	19	51
Yes	18	49
Differences between institutions and pathologists in assessment of venous involvement?		
No	4	11
Yes	33	89

Complications

An increased risk of complications after VR was estimated by 42 (55%) surgeons (Table 1). An increased risk of complications after a resection of the SMV/confluens compared with PV was estimated by 55 (72%) surgeons. Type 3 reconstruction (in the scenario of multiple options) was preferred by 46 (61%) surgeons, followed by 22 (26%) surgeons who preferred Type 1 reconstruction (Fig. 3). Type 4 reconstruction was presumed to carry the highest risk of complications by 45 (59%) surgeons, followed Type 1 reconstruction by 15 (20%) surgeons (Fig. 2B).

The most expected postoperative complication was PV-SMV thrombosis within 90 days after surgery, followed by development of portal hypertension at long-term (Table 1). Some variation in the expected complications due to congestion of the VR within 90 days after surgery existed. Bleeding from the VR within 90 days was the least expected complication.

Technical aspects

A VR was always performed by 57 (75%) surgeons themselves, 22% of surgeons prefer to consult a vascular or transplant surgeon (if available) and 2% of surgeons never perform the VR themselves (Table 3). Clamping for proximal and distal venous control before VR was preferred over vessel loops by 72 (95%) surgeons. The use of a donor vein was preferred over an autologous vein by 14 (18%) surgeons. Heparinization during VR was used by 23 (30%) surgeons. Intraoperative flow measurement in the venous reconstruction was performed by nine (12%) surgeons (accepted flow range: 150-900 mL/min). Clamping of the superior mesenteric artery (SMA) to prevent bowel wall edema during VR was used by 14 (18%) surgeons.

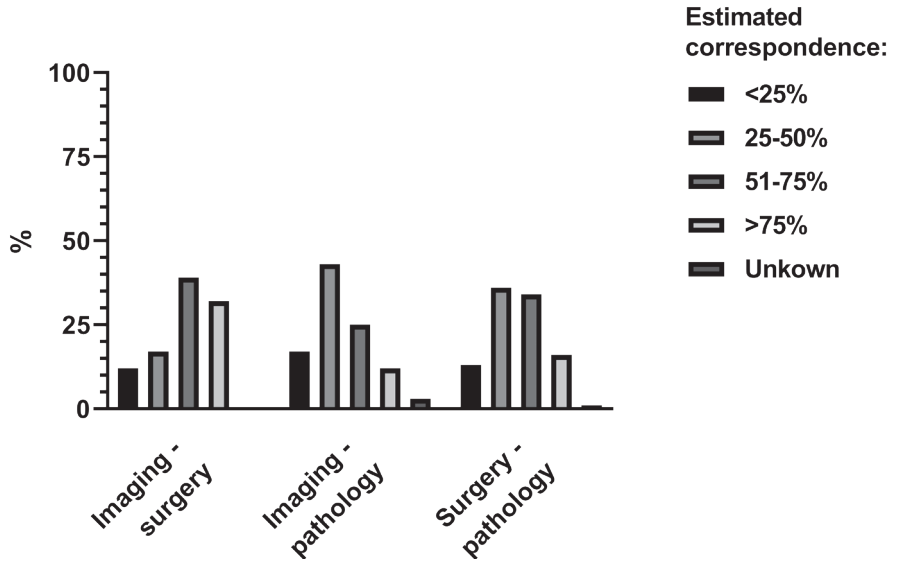

Figure 2. Estimated correspondence between preoperative imaging, findings during surgery and pathological assessment regarding venous involvement.

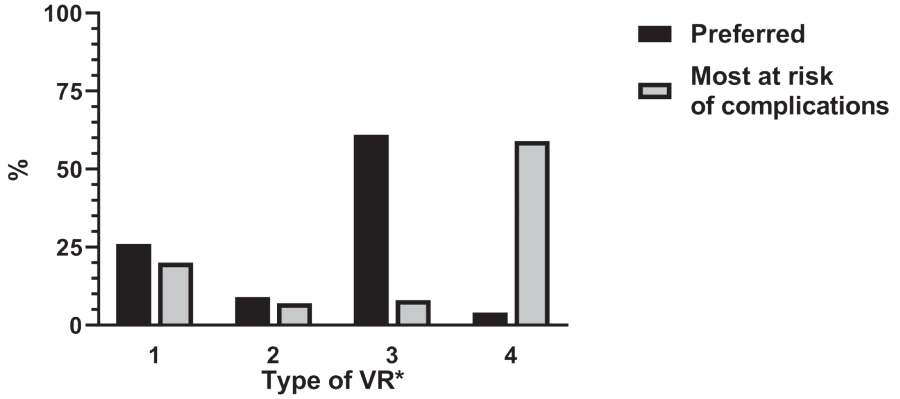

Figure 3. Preferred type of venous resection and presumed most at risk of complications.

Postoperative care

Standard postoperative imaging (ultrasound or computed tomography) for patency control was performed by 41 (54%) surgeons. More than 10 standard thromboprophylaxis regimens were identified when considering type of medication, dosage and duration of prophylaxis. An adjusted thromboprophylaxis regimen following VR (compared to standard) was used by 30 (39%) surgeons

International expert surgeons versus DPCG surgeons

A comparison between international expert and Dutch surgeons is provided in the Supplementary Material. Among international expert surgeons, the estimated percentage of VR was higher, Type 3 VR was more often preferred over Type 1, an increase of the risk of complications after VR was less often expected (namely less PV-SMV thrombosis within 90 days after surgery) and Type 4 VR was presumed to carry a higher risk of complication over Type 1. Furthermore, international expert surgeons surgeons performed the VR more often themselves and performed heparinization more often.

Pathologist-specific survey

Pathological assessment

Tumor infiltration in the wall of the resected vein was always assessed by 28 (78%) pathologists (Table 2). The resection margins of the resected vein were always assessed by 19 (53%) pathologists. The depth of tumor infiltration in the wall of the resected vein was always assessed by 12 (32%) pathologists. Some variation was observed in the extent of sampling to assess tumor infiltration.

Additional stainings for the assessment of the wall of the resected PV-SMV were used by 18 (49%) pathologists. The Elastica von Gieson staining was preferred by 16 (45%) pathologists. Among the reasons not to determine (depth of) tumor infiltration or resection margins of the resected vein: 'not in hospital protocol', 'not relevant for prognosis', 'resected vein not recognized' were mentioned. Variation in daily practice of pathological assessment of the resected vein was expected by 33 pathologists (89%).

International expert pathologists versus DPCG pathologists

A comparison between international expert and Dutch pathologists is provided in the Supplementary Material. Among international expert pathologists, the estimated percentage of VR was higher, assessment of depth of tumor infiltration in the wall of the resected PV-SMV was more often always performed and additional stainings (namely Elastica von Gieson staining) for assessment of the wall of the resected PV-SMV were used less frequently.

Table 3. Technical management of pancreatoduodenectomy with venous involvement by surgeons.

	Total cohort of surgeons	
	N	**%**
Total	**76**	
Do you perform the venous resection and reconstruction yourself?		
No	2	3
If possible, with vasc/tx surgeon	17	22
Yes	57	75
Preference for vascular control before venous resection?		
Vessel loops	3	4
Clamping	72	95
Not specified	1	1
Preference as venous graft?		
Autologous vein	62	82
Donor vein	14	18
Preference as syntethic graft?		
PTFE	15	20
Goretex	10	13
Dacron	2	3
Not specified	49	64
Do you perform heparinization?		
No	53	70
Yes	23	30
Do you perform flow measurement?		
No	67	88
Yes	9	12
Do you perform SMA occlusion to prevent portal congestion		
No	62	82
Yes	14	18
Do you perform standard post-operative imaging?		
No	35	46
Yes	41	54
Do you adjust thromboprophylaxis?		
No	46	61
Yes	30	39

Vasc/tx: vascular/transplant; PTFE: Polytetrafluoroethylene; SMA: superior mesenteric artery

DISCUSSION

This international survey gives insights into the current surgical management and pathological assessment of pancreatoduodenectomy with venous involvement of international surgeons and pathologists. Different perceptions exist between surgeons and pathologists regarding the estimated percentage of pancreatoduodenectomies with VR. Correspondence between preoperative imaging, intraoperative findings and pathology regarding venous involvement was considered to be suboptimal. Half of the surgeons use intraoperative ultrasound to assess venous involvement. Type 3 reconstruction (segmental resection with primary anastomosis) is most popular, followed by Type 1 reconstruction (partial venous excision with direct closure). Half of surgeons expected a higher risk of complications after VR (especially PV-SMV thrombosis). Some surgeons prefer a donor vein over an autologous vein and some surgeons use clamping of the SMA. Heparinization during VR, postoperative imaging and thromboprophylaxis regimens differed substantially. Most pathologists determine whether there is tumor infiltration in the wall of the resected vein. However, only half of the responding pathologists assess the resection margins of the resected vein. Assessment of depth of tumor infiltration differed between pathologists. Only small differences were observed between international expert and Dutch surgeons and pathologists.

Differences in estimated percentage of VR by participating surgeons reflect what is already known in the literature: a VR rate ranging from 6-65%.(8) Regarding venous involvement, the surgeons estimated less correspondence between preoperative imaging-pathology and surgery–pathology than preoperative imaging–surgery. Surgeons find it hard to determine if there is tumor infiltration in the resected vein during surgery and to select the right candidates for VR. The estimated correspondence between preoperative imaging and intraoperative findings might deteriorate in the near future, because of more frequent neoadjuvant treatment.(31) Neoadjuvant chemo -and radiotherapy downstages the tumor, but also induces inflammation and fibrosis, which makes assessment of vessel involvement on preoperative imaging and during surgery less reliable.(9-11) It should be noted that this survey did not include questions regarding types, quality and timing of preoperative imaging or neoadjuvant treatment.

A survey study found that intraoperative ultrasound is underexposed in the training of active Americas Hepato-Pancreato-Biliary Association members and recent graduates. (32) This may explain why 57% of international expert surgeons never use intraoperative ultrasound (DPCG surgeons: 47%). The promising results of intraoperative ultrasound(14-17), have led to the initiation of the ULTRAPANC study within the DPCG (https://www.trialregister.nl/trial/7621) investigating the added value of intraoperative ultrasound in vascular involvement assessment in pancreatic cancer. To distinguish

pancreatic tumor infiltration from inflammatory or fibrotic tissue, other techniques like fluorescence image-guided surgery and intraoperative cytology of the touch smear of the exposed PV-SMV are being investigated.(33-35) These additional tools may decrease the number of patients put at increased risk of complications due to unnecessary VR (i.e. no tumor infiltration in the resected vein and sufficient resection margin). On the other hand, previous studies have suggested improved survival after routine VR which warrants further investigation.(13)

Type 3 reconstruction was most popular in the scenario of multiple options, followed by Type 1 (namely among DPCG surgeons). A donor vein was preferred over an autologous vein for reconstruction by 18% of surgeons. This probably reflects a variety of personal preferences and experience, though might also be influenced by ethical or legislation issues. Several studies have shown an increase of VR over the time, indicating that there should be sufficient exposure in the training program of pancreatoduodenectomy surgeons.(36-38) Most surgeons thought that Type 4 reconstruction carried the highest risk of complications. Several studies about association between type of VR and complications exist.(19, 21, 39, 40) A meta-analysis and a cohort study showed that a prosthetic graft was associated with early PV-SMV thrombosis.(18, 22) This is relevant since early PV-SMV thrombosis (the most expected complication in the survey) is one of the main causes of postoperative mortality and immediate treatment is warranted. (22, 41, 42) Some studies describe the use of intraoperative techniques like clamping of the SMA, heparinization(22) and flow measurement in the venous reconstruction(43), although its role has yet to be determined as the use varied between surgeons. Thromboprophylaxis might decrease the risk of PV-SMV thrombosis following VR, but a meta-analysis of non-randomized studies showed no association between thromboprophylaxis and incidence of thrombosis.(22) Thromboprophylaxis remains a difficult subject as the balance between thrombosis and postoperative hemorrhage is delicate.(44) In this regard, the large variation in postoperative imaging and thromboprophylaxis regimens among surgeons is remarkable in view of the fact that PV-SMV thrombosis is the most expected complication after VR. Future research is needed to identify the optimal technique for VR, postoperative management (including imaging for patency control and thromboprophylaxis) after pancreatoduodenectomy with VR.

The low estimated percentages of VR by pathologists compared to surgeons may for a large part be explained by unrecognized resected vein due to absence or loss of marking of the specimen and insufficient information in the pathology order. Within the DPCG there is increasing awareness of this problem and several proposals have been discussed to standardize pathology orders and reports. The majority of pathologists in the survey determine tumor infiltration in the wall of the resected vein, whereas only half assesses the resection margins of the resected venous wedge or segment. As stated by the ISGPS,

a VR is indicated if a radical resection is possible and thus the resection margins of the VR should be assessed to confirm this. However, the significance of a positive or minimal margin at the resected vein is unclear, let alone the relevance of tumor reaching the tunica intima which suggests possible shedding of tumor into the bloodstream. Assessment of depth of tumor infiltration (27% never, 16% rarely, 24% most often, 32% always) varied between pathologists. This is not surprising, since contemporary literature on the clinical relevance of depth of infiltration is contradicting.(4, 5, 21, 23, 24). According to the ISGPS, depth of vessel infiltration should be classified as tunica adventitia, media and further, or tumor in the intima.(1) It is unclear whether pathologists were involved in the ISGPS statement. The proposed classification is challenging for pathologists as the limits of the tunica adventitia are not easily identified due to peritumoral inflammation.

There are two commonly used grossing techniques (axial slicing and bivalving) for pathological assessment of the pancreatoduodenectomy specimen. There is no evidence in favor of one or the other and the choice is often based on personal preferences and training history.(25) The main advantage of the bivalving technique is the ability to adequately asses the origin of periampullary tumors and assess cystic tumors and their relationship to the ducts, which is less relevant in pancreatic cancer specimens. The bivalving dissection method(45) and the Royal College of Pathologists dataset(46) describe sampling of the resected vein, although without precise sampling directions. The axial dissection method necessitates more samples, with a higher probability of finding an R1 margin, and a more extensive nodal assessment. However, it does not describe sampling of the resected vein.(47, 48) Almost all pathologists expected variation in daily practice regarding the approach of a resected vein. The principal reason for this is the lack of information in pathology orders and communication between the surgeon and pathologist. This emphasizes the need for standardization and completeness of pathology orders. Once the resected vein is always recognized and assessment is standardized, it may become possible to study the clinical and prognostic implications of tumor infiltration in the wall of the resected vein, its resection margins and relationship between tumor infiltration and circulating tumor DNA.

This results of this study should be interpreted in light of some limitations. First, the relatively small sample size. The systematic review of the last decade ensures representation of expert pancreatic surgeons and pathologists and provides insight in the multidisciplinary management on an international level. Due to the small sample size, however, no subgroup analyses were performed per continent. Second, responses are preferences and perceptions of individuals and were not confirmed by patient data. Lastly, when interpreting the comparison between international experts and Dutch surgeons and pathologists, one must realize that the international experts are mostly

from high(er) volume institution and have been involved in research on this topic as a result of the selection of these experts from the literature.

Nowadays, pancreatoduodenectomy with venous involvement is a small but growing part of clinical practice and therefore collaboration is pivotal to gain evidence and improve outcomes. To provide more insight in the clinical impact of pancreatoduodenectomy with venous involvement, the authors initiated the MULTI-VERS PROJECT (https://www.trialregister.nl/trial/6775).

In conclusion, this international survey shows variations in the surgical management and pathological assessment of pancreatoduodenectomy with venous involvement. This highlights the lack of high-level evidence and emphasizes the need for further research on imaging modalities to improve patient selection for VR, surgical techniques, postoperative management, the prognostic relevance and standardized pathology assessment of tumor infiltration, depth of tumor infiltration and resection margins of the resected vein.

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SUPPLEMENTARY MATERIAL

Table S1. Clinical management of pancreatoduodenectomy with venous involvement by surgeons.

	International expert surgeons		DPCG surgeons		
	N	**%**	**N**	**%**	**P-value**
Total	59		17		
Continent					
Europe	34	58	17	100	-
America	13	22	0		
Asia/Oceanie	12	20	0		
Estimated percentage of venous resection?					
≥10%	13	22	6	35	0.178
11-20%	27	46	10	59	
21-40%	16	27	1	6	
>40%	3	5	0		
Do you use per-operative imaging (ultrasound)?					
Never	35	59	8	47	0.657
Selected cases	18	31	7	41	
Always	6	10	2	12	
Increased risk of complications?					
Venous resection					
No	31	53	3	18	0.011
Yes	28	47	14	82	
Confluens/SMV versus the PV?					
No	18	31	3	18	0.296
Yes	41	69	14	82	
Estimated incidence of:					
Post-operative thrombosis?*					
<5%	30	51	2	12	<0.001
5-10%	26	44	6	35	
>10%	3	5	9	53	
Post-operative portal hypertension at long-term?					
<5%	34	58	8	47	0.720
5-10%	15	25	5	29	
>10%	10	17	4	24	

Table S1. Continued

Post-operative bleeding of vascular reconstruction?*					
<5%	57	97	15	88	0.151
5-10%	2	3	1	6	
>10%	0	0	1	6	
Post-operative complications due to congestion?*					
<5%	49	83	7	41	0.002
5-10%	7	12	6	35	
>10%	3	5	4	24	

*<90 days after surgery

Table S2. Assessment of pancreatoduodenectomy specimen with venous involvement by pathologists.

	International expert pathologists		DPCG pathologists		
	N	**%**	**N**	**%**	**P-value**
Total	18	49	19	51	-
Continent					
Europe	10	56	19	100	-
America	2	11	0		
Asia/Oceanie	5	28	0		
Unknown	1	6	0		
Estimated percentage of venous resection?					
<5%	1	6	9	47	<0.001
5-10%	5	28	10	53	
11-20%	3	17	0		
>20%	9	50	0		
Do you assess tumor infiltration in the resected vein?					
Never	0	0	3	16	0.243
Rarely	1	6	0		
Most often	3	17	2	11	
Always	14	78	14	74	
Extent of assessment					
None	0	0	3	16	0.206
Most suspected part	9	50	9	47	
Complete	9	50	6	32	
Not standardized	0		1	5	

Table S2. Continued

Do you assess depth of tumor infiltration in the resected vein?					
Never	2	11	8	42	0.087
Rarely	2	11	4	21	
Most often	6	33	3	16	
Always	8	44	4	21	
Extent of assessment					
None	2	11	8	42	0.064
Most suspected	9	50	4	21	
Complete	7	39	7	37	
Do you assess the resection margins of the resected vein?					
Never	2	11	4	21	0.403
Rarely	1	6	3	16	
Most often	5	28	2	11	
Always	10	56	10	53	
Extent of assessment					
None	2	11	4	21	0.485
Most suspected	5	28	7	37	
Complete	11	61	8	42	
Do you use additional stainings for assessment of the resected vein?					
No	12	67	7	37	0.070
Yes	6	33	12	63	
Differences between institutions and pathologists?					
No	3	17	1	5	0.340
Yes	15	83	18	95	

Table S3. Technical management of pancreatoduodenectomy with venous involvement by surgeons.

	International expert surgeons		DPCG surgeons		
	N	**%**	**N**	**%**	**P-value**
Total	**59**		**17**		
Do you perform the venous resection and reconstruction yourself?					
No	1	2	1	6	0.056
If possible, with vasc/tx surgeon	10	17	7	41	
Yes	48	81	9	53	
Preference for vascular control before venous resection?					
Vessel loops	2	3	1	6	0.151
Clamping	57	97	15	88	
Not specified	0		1	6	
Preference as venous graft?					
Autologous vein	46	78	16	94	0.171
Donor vein	13	22	1	6	
Preference as syntethic graft?					
PTFE	14	24	1	6	0.050
Goretex	10	17	0		
Dacron	1	2	1	6	
Not specified	34	58	15	88	
Do you perform heparinization?					
No	38	64	15	88	0.060
Yes	21	36	2	12	
Do you perform flow measurement?					
No	51	86	16	94	0.388
Yes	8	14	1	6	
Do you perform SMA occlusion to prevent portal congestion					
No	47	80	15	88	0.422
Yes	12	20	2	12	
Do you perform standard post-operative imaging?					
No	25	42	10	59	0.231
Yes	34	58	7	41	
Do you adjust thromboprophylaxis?					
No	34	58	12	71	0.335
Yes	25	42	5	29	

Vasc/tx: vascular/transplant

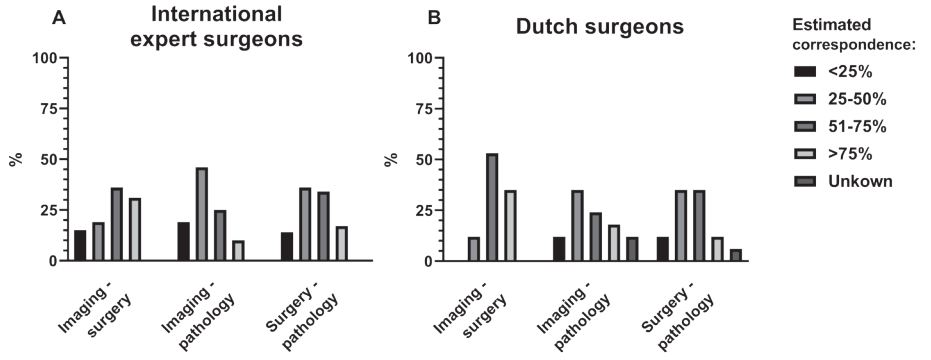

Figure S1. Estimated correspondence between preoperative imaging, findings during surgery and pathological assessment regarding venous involvement.

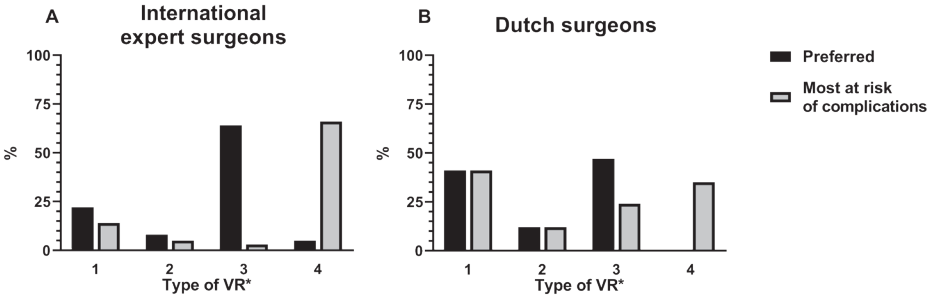

Figure S2. Preferred type of venous resection and presumed most at risk of complications. **Type 1= partial venous excision with direct closure; Type 2= partial venous excision with patch reconstruction; Type 3= segmental resection with primary anastomosis; Type 4=segmental resection with interposed venous conduit and at least two anastomoses.*

CHAPTER 6

Venous wedge and segment resection during pancreatoduodenectomy for pancreatic cancer: impact on short- and long-term outcomes in a nationwide cohort analysis

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ABSTRACT

Background: Venous resection is increasingly performed during pancreatic surgery, while results of studies on short- and long-term outcomes are contradictory. The aim of this study was to evaluate the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity and overall survival.

Methods: This nationwide retrospective cohort study included all patients who underwent pancreatoduodenectomy for pancreatic cancer in 18 centres (2013-2017).

Results: In total, 1311 patients were included of whom 17 per cent underwent wedge resection and 10 per cent segmental resection. Patients with segmental resection had more major morbidity (39 versus 20 versus 23 per cent; *P*<0.001) and portal or superior mesenteric vein thrombosis (18 versus 5 versus 1 per cent; *P*<0.001) and worse overall survival (median 12 versus 16 versus 20 months; *P*<0.001) as compared to patients with wedge and without venous resection. At multivariable analysis, patients with segmental resection had more major morbidity (odds ratio=1.93, 95 per cent CI=1.20-3.11) and worse overall survival (hazard ratio=1.40, 95 per cent CI=1.10-1.78) as compared to patients without venous resection, whereas patients with wedge resection did not. In patients who received neoadjuvant therapy, overall survival showed no difference between patients with segmental, wedge and without venous resection (median 32 versus 25 versus 33 months; *P*=0.47), although the rate of major morbidity was different (52 versus 19 versus 21 per cent; *P*=0.012).

Conclusion: This nationwide study found that short- and long-term outcomes are worse in patients with segmental resection, compared to patients with wedge and without venous resection.

INTRODUCTION

Pancreatic cancer is one of the few types of cancer for which the survival rate has barely improved in the last decades.[1] Radical tumour resection preceded or followed by chemo(radio)therapy is the current standard treatment for patients with pancreatic cancer.[2, 3] The International Study Group of Pancreatic Surgery (ISGPS) suggests that a partial resection of the portal or superior mesenteric vein (PV-SMV) should be performed in case of suspected involvement in order to achieve a radical resection.[4] The use of venous resection during pancreatoduodenectomy is increasing and is expected to increase further with the use of neoadjuvant therapy.[5-8]

In an international survey, the authors recently found that most pancreatic surgeons prefer a venous segment resection with primary anastomosis over a partial venous wedge resection, because of a lower perceived risk of complications.[9] Literature regarding complications after different types of venous resection is contradicting.[8, 10-12] A recent meta-analysis of mostly single centre observational studies showed that venous resection is associated with increased mortality and worse survival.[13] Data on type of venous resection was not available. Nationwide studies with contemporary data representing current clinical practice are lacking.

The aim of this nationwide study was to evaluate the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival.

METHODS

Study design and patient selection

This nationwide retrospective cohort study included all 18 centres (N=18) of the multidisciplinary Dutch Pancreatic Cancer Group (DPCG).[14] All patients, registered in the mandatory, prospective, nationwide Dutch Pancreatic Cancer Audit (DPCA)[15], that underwent pancreatoduodenectomy for pancreatic adenocarcinoma (postoperative pathological diagnosis) from 2013 through 2017 were included. A waiver for informed consent was issued by the Medical Ethics Committee of the Leiden University Medical Centre (G18.103) due to the retrospective nature. The study is reported in accordance with the STROBE criteria.[16]

Data collection

Data were requested from the DPCA. These data included baseline, intraoperative, postoperative, and histopathological characteristics. Additional data were manually extracted from the patients' medical records (e.g. type of venous resection, blood loss, duration of surgery, PV-SMV thrombosis, tumour invasion in resected vein, lymphangio invasion, perineural invasion, follow-up characteristics).

Definitions

The type of venous resection was scored following the ISGPS classification: type 1: partial venous excision with direct suture closure (venorrhaphy); type 2: partial venous excision using a patch; type 3: venous segment resection with primary venovenous anastomosis; and type 4: venous segment resection with interposed venous conduit and at least two anastomoses.[4] For current analysis, type 1 and type 2 resections were categorized as "wedge resection", and type 3 and type 4 resections were categorized as "segmental resection".

Venous involvement on preoperative imaging was defined as absence or presence of a fat plane between the tumour and PV-SMV. Resectability was defined according to the DPCG criteria: resectable (tumour without arterial involvement and with venous involvement <90°), borderline resectable (tumour with arterial involvement <90°and/or venous involvement 90°-269° without occlusion), locally advanced (tumour with arterial involvement ≥90° and/or venous involvement ≥270° or occlusion). Neoadjuvant preoperative therapy was categorized as no/yes, regardless of type, duration and dose of chemo(radio)therapy. Neoadjuvant therapy was mainly administered according the protocol of the PREOPANC trial[17] in which patients with resectable and borderline resectable disease were included (preoperative chemoradiotherapy, which consisted of 3 courses of gemcitabine, the second combined with 15×2.4 Gy radiotherapy) and occasionally outside this trial setting at discretion of the treating physicians. Additional organ resection was defined as any additional organ resection not including standard pancreatoduodenectomy.[18] Pancreatic surgery–specific complications were classified in accordance with ISGPS criteria. Only grade B and grade C complications were reported, as these complications are considered clinically relevant.[19-24] Postoperative PV-SMV thrombosis within 30 days following surgery was scored based on imaging studies which were performed at discretion of the attending physician. The Clavien-Dindo classification was scored within 30 days following surgery and grade ≥III was considered as major morbidity.[25] Postoperative mortality was defined as death within 90 days following surgery, unless the cause of death was clearly disease-related (e.g., early recurrence or metastasis) and not surgery-related.[26] Textbook Outcome was defined by the absence of postoperative pancreatic fistula, bile leak, postpancreatectomy haemorrhage (all ISGPS grade B and C), major morbidity, readmission and postoperative

mortality.[27] The eighth edition of the TNM classification was used for histological classification.[28] An R1 resection margin was defined as the presence of tumour cells within 1 mm of the resection margin.[29] Due to the inclusion of patients with neoadjuvant therapy, overall survival was calculated as the time in months between the start of treatment (day of surgery or start of neoadjuvant therapy) and the date of death (or last follow-up visit) and was truncated at 48 months.

Outcomes and comparisons

The primary outcomes of this study were major morbidity (Clavien-Dindo grade ≥III) and overall survival (since start of treatment). The secondary outcomes were postoperative characteristics: postoperative mortality, PV-SMV thrombosis, postoperative pancreatic fistula, postpancreatectomy haemorrhage, bile leakage, delayed gastric emptying, chyle leak, pneumonia, wound infection, relaparotomy, radiological intervention, (duration of) Intensive Care Unit admission, (duration of) hospital stay, readmission, Textbook Outcome and adjuvant therapy; and histopathological characteristics: resection margin status, tumour invasion in the resected vein, tumour size on pathology, pN-stage, pM-stage, tumour differentiation grade, lymphangio invasion and perineural invasion.

Patients were analysed by category of venous resection: without venous resection, wedge and segmental resection. Subgroup analysis was performed by patients who received neoadjuvant therapy.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Continuous variables are presented as the mean with standard deviation (SD) or the median with interquartile range (IQR), depending on the distribution. Categorical variables are presented as frequencies with percentages. Continuous variables were compared using the Mann-Whitney *U* test or Kruskal-Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact test. Missing data for multivariable analysis (body mass index (BMI), Eastern Cooperative Oncology Group, aspect of the pancreatic remnant, diameter of the pancreatic duct, blood loss, duration of surgery, tumour size on pathology, pN-stage, tumour differentiation grade, lymphangio invasion, perineural invasion) were imputed 25 times based on relevant prognostic factors (venous resection, sex, age, biliary drainage, neoadjuvant therapy, American Society of Anesthesiologists (ASA) score, minimally invasive procedure, arterial resection, additional organ resection, resection margin status, pM-stage) and the outcome variables (major morbidity and overall survival). Log-transformation was performed for not-normally distributed variables.[30] Multivariable binary logistic regression analysis was performed to assess the impact of category of venous resection on major morbidity and adjust for potential confounders. Overall

survival was reported as the median with 95 per cent CI, and Kaplan-Meier curves and log-rank tests were used to compare groups. A multivariable Cox proportional hazards model was used to assess the impact of type venous resection on overall survival and adjust for potential confounders. A sensitivity analysis was performed for the impact of category of venous resection on major morbidity and overall survival with complete cases, without multiple imputation, to show the robustness of the results. A two-sided *P*-value <0.05 was considered statistically significant, and *P*-values ≥0.05 were rounded to two decimal places.

RESULTS

Baseline characteristics

In total, 1311 patients that underwent pancreatoduodenectomy for pancreatic cancer were included of which 351 (27 per cent) underwent a venous resection. Baseline characteristics are shown in Table 1. The median age was 68 (61-74) years, and 734 patients (56 per cent) were male. Of the patients with venous resection, 227 (65 per cent) underwent wedge resection (196 patients with type 1 and 31 patients with type 2) and 124 (35 per cent) underwent segmental resection (97 patients with type 3, 27 patients with type 4). Several baseline characteristics differed significantly between the categories of venous resection: BMI, preoperative resectability status, minimally invasive surgery, texture of the pancreatic remnant, pancreatic duct diameter, additional resection, duration of surgery and blood loss during surgery. Patients with segmental resection more often had venous involvement on preoperative imaging as compared to patients with wedge resection and without venous resection (93 [75 per cent] versus 134 [59 per cent] versus 252 [26 per cent] patients; *P*<0.001). Patients with segmental resection received more often neoadjuvant therapy as compared to patients with wedge resection and without venous resection (23 [19 per cent] versus 21 [9 per cent] versus 57 [6 per cent] patients; *P*=0.012).

Over the study period, the annual rate of venous resection increased from 20 to 32 per cent (*P*=0.001; Figure S1). Variation was observed regarding the number of pancreatoduodenectomies (range 38-129), the percentage venous resection (range 10-53 per cent) and segmental/wedge resection ratio (range 0-6) per centre during the study period (Figure S2).

Table 1. Baseline characteristics by category of venous resection

		Without venous resection	Wedge resection	Segmental resection	*P*-value
Total		960 (73.2)	227 (17.3)	124 (9.5)	-
Sex	**Male**	554 (57.7)	115 (50.7)	65 (52.4)	0.11
	Female	406 (42.3)	112 (49.3)	59 (47.6)	
Age in years, median (IQR)		68 (61-74)	68 (61-73)	69 (62-74)	0.73
BMI in kg/m², mean (SD)		25.1 (4.2)	24.5 (3.9)	23.8 (3.4)	0.002
ECOG	**0-1**	862 (89.8)	196 (86.3)	112 (90.3)	0.31
	2-4	98 (10.2)	31 (13.7)	12 (9.7)	
Preoperative biliary drainage		542 (56.5)	135 (59.5)	68 (54.8)	0.64
Venous involvement on preoperative imaging		252 (26.3	134 (59.0)	93 (75.0)	<0.001
Preoperative resectability status	**Resectable**	780 (83.3)	126 (56.8)	46 (38.3)	<0.001
	Borderline resectable	113 (12.1)	76 (34.2)	62 (51.7)	
	Locally advanced	43 (4.6)	20 (9.0)	12 (10.0)	
Neoadjuvant therapy		57 (5.9)	21 (9.3)	23 (18.5)	<0.001
Type of neoadjuvant therapy	**Chemoradiotherapy**	33 (57.9[b])	12 (57.1[b])	13 (56.5[b])	0.99
	Chemotherapy	24 (42.1[b])	9 (42.9[b])	10 (43.5[b])	
ASA score	**I-II**	742 (77.3)	176 (77.5)	97 (78.2)	0.97
	III-IV	218 (22.7)	51 (22.5)	27 (21.8)	
Minimally invasive procedure		109 (11.4)	10 (4.4)	4 (3.2)	<0.001
Type of surgery	**Classic Whipple**	347 (36.1)	75 (33.0)	53 (42.7)	0.45
	PPPD	591 (61.6)	145 (63.9)	68 (54.8)	
	PRPD	22 (2.3)	7 (3.1)	3 (2.4)	
Texture pancreatic remnant	**Normal/Soft**	451 (47.0)	79 (34.8)	38 (30.6)	<0.001
	Fibrotic/Hard	509 (53.0)	148 (65.1)	86 (69.4)	

Table 1. Continued

Pancreatic duct diameter in mm, median (IQR)	5 (3-8)	6 (4-9)	6 (4-9)	<0.001
Arterial resection	9 (0.9)	5 (2.2)	3 (2.4)	0.16
Additional resection	51 (5.3)	9 (4.0)	13 (10.5)	0.031
Duration of surgery in min, median (IQR)	295 (239-377)	344 (278-423)	388 (321-458)	<0.001
Blood loss during surgery in mL, median (IQR)	600 (350-1000)	700 (450-1100)	1200 (600-2000)	<0.001

IQR: interquartile range; BMI: body mass index; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; PPPD: pylorus-preserving pancreatoduodenectomy; PRPD: pyloric ring pancreatoduodenectomy
Values are frequencies (per cent) unless indicated otherwise
Missing data was imputed: BMI (N=8), ECOG (N=6), texture of pancreatic remnant (N=103), pancreatic duct diameter (N=256), duration of surgery (N=136), blood loss (N=148). Missing data not imputed: preoperative resectability status (N=33).
[a] According to the Dutch Pancreatic Cancer Group criteria
[b] Percentage is based on the number of patients who received neoadjuvant therapy

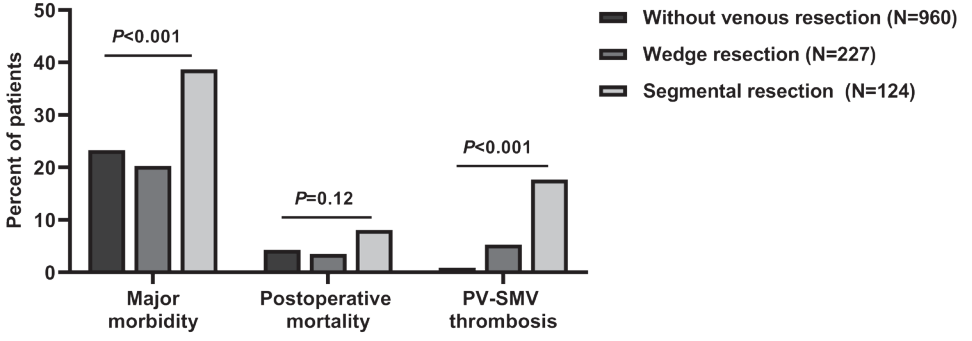


Figure 1. Major morbidity (Clavien-Dindo grade ≥III), postoperative mortality and portal vein-superior mesenteric vein thrombosis after pancreatoduodenectomy for pancreatic cancer by category of venous resection

Primary outcomes

Major morbidity

Patients with segmental resection had a higher rate of major morbidity as compared to patients with wedge resection and without venous resection (48 [39 per cent] versus 46 [20 per cent] versus 224 [23 per cent] patients; *P*<0.001; Figure 1). Multivariable analysis for major morbidity is shown in Table 2. Segmental resection was an independent predictor for major morbidity (odds ratio (OR): 1.93, 95 per cent CI: 1.20-3.11), whereas wedge resection was not (OR: 0.95, 95 per cent CI: 0.64-1.40). A sensitivity analysis with complete cases showed similar results (segmental resection: OR: 2.11, 95 per cent CI: 1.11-3.99; wedge resection: OR: 0.84, 95 per cent CI: 0.49-1.44; Table S1). Major morbidity rates were not different between patients with and without venous involvement on preoperative imaging for wedge (30 [22 per cent] versus 16 [17 per cent] patients; P=0.34) and segmental resection (13 [42 per cent] versus 35 [38 per cent] patients; P=0.67).

Overall survival

Patients with segmental resection had worse overall survival (median: 12, 95 per cent CI: 9-15 months) as compared to patients with wedge resection (median: 16, 95 per cent CI: 12-20 months) and without venous resection (median: 20, 95 per cent CI: 18-22 months; *P*<0.001; Figure 2). Multivariable analysis for overall survival is shown in Table 2. Segmental resection was an independent predictor for worse overall survival (hazard ratio (HR): 1.40, 95 per cent CI: 1.10-1.78), whereas this could not be demonstrated for wedge resection (HR: 1.04, 95 per cent CI: 0.86-1.27). A sensitivity analysis with complete cases showed similar results (segmental resection: HR: 1.35, 95 per cent CI: 1.02-1.77; wedge resection: HR: 0.97, 95 per cent CI: 0.77-1.23; Table S1). A post-hoc analysis, which also adjusted for the use of adjuvant therapy in patients without postoperative mortality, showed similar results (segmental resection: HR: 1.34, 95 per cent CI: 1.04-1.72; wedge resection: HR: 1.11, 95 per cent CI: 0.91-1.36; Table S2).

Secondary outcomes

Postoperative characteristics

Postoperative mortality did not differ significantly between patients with segmental resection, with wedge resection and without venous resection (10 [8 per cent] versus 8 [4 per cent] versus 4 [4 per cent] patients; *P*=0.12; Figure 1). Patients with segmental resection had a higher rate of PV-SMV thrombosis as compared to patients with wedge resection and without venous resection (22 [18 per cent] versus 12 [5 per cent] versus 9 [1 per cent] patients; *P*<0.001). Patients with segmental resection had a higher rate of relaparotomy (23 [19 per cent] versus 13 [6 per cent] versus 69 [7 per cent] patients; *P*<0.001), chyle leak, radiological intervention, Intensive Care Unit admission and readmission, a longer hospital stay and a lower rate of Textbook Outcome as compared to patients with wedge resection and without venous resection (Table 3).

Table 2. Multivariable analysis of major morbidity (Clavien-Dindo grade ≥III) and overall survival by category of venous resection

		Major morbidity			Overall survival		
		Odds ratio	95 per cent CI	*P*-value	Hazard ratio	95 per cent CI	*P*-value
Category of venous resection[a]	**Wedge resection**	0.95	0.64-1.40	0.79	1.04	0.86-1.27	0.68
	Segmental resection	1.93	1.20-3.11	0.007	1.40	1.10-1.78	0.007
Sex[b]	**Female**	1.06	0.81-1.39	0.68	1.01	0.87-1.17	0.95
Age (years)[c]		1.00	0.99-1.02	0.95	1.02	1.01-1.02	0.001
BMI (kg/m²)[c]		1.01	0.98-1.05	0.41	0.99	0.97-1.01	0.25
ECOG[d]	**2-4**	0.80	0.51-1.28	0.36	0.87	0.68-1.11	0.25
Preoperative biliary drainage[a]		0.90	0.69-1.18	0.44	-	-	-
Preoperative resectability status[e]	**Borderline resectable**	0.89	0.62-1.28	0.54	-	-	-
	Locally advanced	0.46	0.23-0.91	0.024	-	-	-
Neoadjuvant therapy[a]		1.46	0.88-2.43	0.15	0.90	0.66-1.22	0.51
ASA score[f]	**III-IV**	1.68	1.23-2.31	0.001	1.45	1.22-1.73	<0.001
Minimally invasive procedure[a]		1.49	0.94-2.36	0.09	-	-	-
Arterial resection[a]		1.59	0.55-4.55	0.39	-	-	-
Additional resection[a]		1.59	0.92-2.73	0.10	-	-	-
Texture pancreatic remnant[g]	**Fibrotic/Hard**	0.79	0.60-1.05	0.11	-	-	-
Pancreatic duct diameter (mm)[c]		0.94	0.90-0.98	0.005	-	-	-
Duration of surgery (min)[c]		1.00	1.00-1.00	0.55	-	-	-
Blood loss (mL)[c]		1.00	1.00-1.00	<0.001	-	-	-
Resection margin status[h]	**R1**	-	-	-	1.26	1.08-1.48	0.004
Tumour size on pathology (mm)[c]		-	-	-	1.01	1.00-1.02	0.008

Table 2. Continued

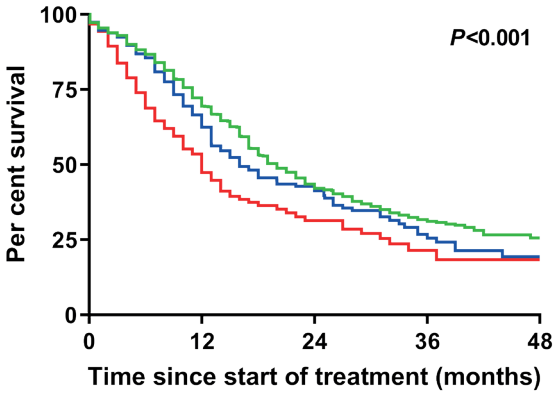
pN-stage[i]	**N1**	-	-	-	1.11	0.92-1.36	0.29
	N2	-	-	-	1.45	1.17-1.80	0.001
pM-stage[j]	**M1**	-	-	-	1.22	0.79-1.89	0.36
Tumour differentiation grade[k]	**Moderate**	-	-	-	1.55	1.17-2.04	0.002
	Poor/Undifferentiated	-	-	-	2.26	1.69-3.02	<0.001
Lymphangio invasion[a]		-	-	-	1.10	0.92-1.31	0.30
Perineural invasion[a]		-	-	-	1.21	0.94-1.36	0.29

CI: confidence interval; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists.

[a] Reference category: 'Without/No'
[b] Reference category: 'Male'
[c] Continuous variable
[d] Reference category: '0-1'
[e] Reference category: 'Resectable'
[f] Reference category: 'I-II'
[g] Reference category: 'Normal/soft'
[h] Reference category: 'R0'
[i] Reference category: 'N0'
[j] Reference category: 'M0'
[k] Reference category: 'Good'

Vascular complications (PV-SMV thrombosis or haemorrhage) were the indication for relaparotomy in 18 out of 23 [78 per cent] patients with segmental resection (Table S3).

The rate of adjuvant therapy was lower in patients with segmental resection as compared to patients with wedge resection and without venous resection (66 [58 per cent] versus 169 [78 per cent] versus 646 [71 per cent] patients; *P*<0.001). The same difference was found in the subgroup of patient without neoadjuvant chemotherapy and postoperative mortality (51 [54 per cent] versus 149 [76 per cent] versus 607 [71 per cent] patients; *P*<0.001).



Numbers at risk					
Without venous resection	959	579	250	108	45
Wedge resection	227	131	55	20	6
Segmental resection	124	60	23	7	2

Figure 2. Kaplan-Meier curves of overall survival after pancreatoduodenectomy for pancreatic cancer by category of venous resection

Histopathological characteristics

Patients with segmental and wedge resection had a higher rate of R1 resections compared to patients without venous resection (80 [65 per cent] versus 147 [65 per cent] versus 441 [46 per cent] patients; *P*=0.001; Table 3). Data on tumour invasion in the resected vein was available for 207 patients (59 per cent). Tumour invasion did not differ between patients with wedge and segmental resection (69 [58 per cent] versus 58 [67 per cent] patients; *P*=0.18). Patients with segmental resection had larger tumours as compared to patients with wedge resection and without venous resection (median 35 versus 31 versus 30 mm; *P*<0.001).

Table 3. Postoperative and histopathological characteristics by category of venous resection

		Without venous resection	Wedge resection	Segmental resection	*P*-value
Postoperative characteristics					
Postoperative pancreatic fistula		87 (9.1)	11 (4.8)	7 (5.6)	0.07
Postpancreatectomy haemorrhage		72 (7.5)	9 (4.0)	12 (9.7)	0.09
Bile leakage		29 (3.0)	5 (2.2)	4 (3.2)	0.78
Delayed gastric emptying		160 (16.7)	31 (13.7)	25 (20.3)	0.26
	Missing	1	0	1	
Chyle leak		25 (2.6)	12 (5.3)	18 (14.5)	<0.001
Pneumonia		58 (6.0)	10 (4.4)	9 (7.3)	0.51
Wound infection		100 (10.4)	19 (8.4)	11 (8.9)	0.60
Relaparotomy		69 (7.2)	13 (5.7)	23 (18.5)	<0.001
Radiological intervention		135 (14.1)	21 (9.3)	23 (18.5)	0.041
ICU admission		92 (9.6)	23 (10.1)	27 (21.8)	<0.001
Duration of ICU admission in days[a], median (IQR)		4 (2-12)	6 (3-13)	5 (2-13)	0.77
	Missing	5	2	1	
Duration of hospital stay in days[b], median (IQR)		11 (8-16)	10 (8-14)	15 (11-23)	<0.001
	Missing	2	1	0	
Readmission[b]		134 (14.6)	32 (14.6)	35 (30.7)	<0.001
Textbook Outcome		638 (66.5)	159 (70.0)	60 (48.4)	<0.001
Adjuvant therapy[b]		646 (71.2)	169 (77.5)	66 (58.4)	0.001
	Missing	12	1	1	
Histopathological characteristics					

Table 3. Continued

Resection margin status	**R0**	519 (54.1)	80 (35.2)	44 (35.5)	<0.001
	R1	441 (45.9)	147 (64.8)	80 (64.5)	
Tumour invasion in resected vein		-	69 (57.5)	58 (66.7)	0.18
	Missing		107	37	
Tumour size on pathology in mm, median (IQR)		30 (22-38)	31 (25-40)	35 (27-41)	<0.001
pT-stage	**T1**	135 (14.1)	19 (8.4)	11 (8.9)	<0.001
	T2	590 (61.8)	141 (62.4)	62 (50.4)	
	T3	214 (22.4)	55 (24.3)	45 (36.6)	
	T4	16 (1.7)	11 (4.9)	5 (4.1)	
pN-stage	**N0**	255 (26.6)	59 (26.0)	34 (27.4)	0.97
	N1	381 (39.7)	86 (37.9)	49 (39.5)	
	N2	324 (33.8)	82 (36.1)	41 (33.1)	
pM-stage	**M0**	936 (97.5)	222 (97.8)	120 (96.8)	0.84
	M1	24 (2.5)	5 (2.2)	4 (3.2)	
Tumour differentiation grade	**Good**	135 (14.0)	27 (11.9)	14 (11.3)	0.78
	Moderate	543 (56.6)	123 (54.2)	70 (56.5)	
	Poor/Undifferentiated	282 (29.4)	77 (33.9)	40 (32.3)	
Lymphangio invasion		518 (54.0)	144 (63.4)	73 (58.9)	0.49
Perineural invasion		792 (82.5)	208 (91.6)	104 (83.9)	0.95

ICU: Intensive Care Unit; IQR: interquartile range
Values are frequencies (per cent) unless indicated otherwise
Missing data was imputed: pN-stage (N=1), pT-stage and tumour size on pathology (N=7), tumour differentiation grade (N=125), lymphangio invasion (N=225), perineural invasion (N=147).
[a] Patients admitted to the ICU
[b] Patients without postoperative mortality

Patients who received neoadjuvant therapy

In total, 101 (8 per cent) patients received neoadjuvant therapy. Baseline characteristics and histopathological characteristics were largely comparable between the categories of venous resection (Table S4). Patients with segmental resection had a higher rate of major morbidity (12 [52 per cent] versus 4 [19 per cent] versus 12 [21 per cent] patients; *P*=0.012), postoperative mortality (4 [17 per cent] versus 0 [0 per cent] versus 4 [7 per cent] patients; *P*=0.10) and PV-SMV thrombosis (6 [26 per cent] versus 1 [5 per cent] versus 1 [2 per cent] patients; *P*=0.001) as compared to patients with wedge resection and without venous resection. At multivariable analysis, segmental resection was an independent predictor for major morbidity (OR: 3.75, 95 per cent CI: 1.26-11.17), whereas this could not be demonstrated for wedge resection (OR: 0.84, 95 per cent CI: 0.23-3.10; Table S5).

Overall survival showed no difference between patients with segmental resection (median: 32, 95 per cent CI: 19-45 months), wedge resection (median: 25, 95 per cent CI: 6-44 months) and without venous resection (median: 33, 95 per cent CI: 21-45 months; *P*=0.47; Figure S3). At multivariable analysis, segmental and wedge resection both did not predict overall survival (HR: 1.21, 95 per cent CI: 0.55-2.27; HR: 1.16, 95 per cent CI: 0.53-2.51; respectively, Table S5).

DISCUSSION

This nationwide study of 1311 patients undergoing pancreatoduodenectomy for pancreatic cancer demonstrated that patients with venous segment resection had a doubling of the major morbidity rate and an 17 per cent increased risk on PV-SMV thrombosis compared to patients without venous resection. The segmental resection group had a worse overall survival compared to wedge resection and without venous resection (median 12 versus 16 versus 20 months), which remained after correction for clinical and pathological factors. In patients who received neoadjuvant therapy, overall survival showed no difference between patients with segmental, wedge and without venous resection (median 32 versus 25 versus 33 months), whereas major morbidity (52 per cent versus 19 per cent versus 21 per cent) and postoperative mortality (17 per cent versus 0 per cent versus 7 per cent) were higher after venous segment resection.

In contrast with the found preference for a segmental resection in the international survey, more patients underwent a wedge resection (65 per cent) compared to a segmental resection (35 per cent). The choice to perform a venous resection and reconstruction type is multifactorial and based on surgeon's preference and skills, as well as the perceived circumference and length of vein involvement.[31] Little is known what exactly drives the surgeon's preference with regard to choice of type of venous reconstruction.[9]

Large studies focusing on outcome and type of venous resection are sparse. The largest study (977 venous resections) used the NSQIP database to show that, as compared to without venous resection, direct repair (72 per cent) was associated with higher morbidity and graft repair (28 per cent) was associated with higher morbidity and mortality.[8] Unfortunately, comparison with the present study is difficult since the study did not use ISGPS venous resection definition and Clavien-Dindo classification. Another large study (229 venous resections) showed no difference in morbidity, mortality and survival between types of venous resection.[11] In contrast to a single centre study of 249 patients (period 2000-2010)[32], patients with and without venous involvement on preoperative imaging and venous resection had comparable major morbidity rates. Based on the available data, it can only be speculated what the exact reasons were for the higher major morbidity after segmental resection. Previously, vascular complications have shown to be the main causes of postoperative mortality[33] and were the main indication for relaparotomy in these patients. There are no studies available investigating the association between outcome and the number or proportion of venous resections performed at an institution. This was not investigated here since only patients with pancreatoduodenectomy for pancreatic cancer were included and there was no clear association between the volume of pancreatoduodenectomies, proportion of venous resection or category of venous resection. Future research should focus on identifying optimal venous reconstruction techniques and protocols (e.g. clamping time, length of vein resected, type of conduit, preservation or ligation of the splenic vein, heparinization etc.).

The rate of PV-SMV thrombosis after segmental resection (18 per cent) was higher compared to other studies (~8 per cent).[11, 34, 35] The current study had no patient-level data on thromboprophylaxis to study the effect on PV-SMV thrombosis. However, only 29 per cent of Dutch surgeons adjusted thromboprophylaxis following venous resection (some start a platelet aggregation inhibitor or increase the dose of low molecular weight heparin).[9] A previous meta-analysis found no differences in PV-SMV thrombosis in patients with and without thromboprophylaxis.[34] Moreover, intensified thromboprophylaxis might result in more haemorrhages[36], reflecting the fragile balance between thromboprophylaxis, postoperative thrombosis, and haemorrhage in pancreatic surgery.

Segmental resection, but not wedge resection, was a predictor for worse overall survival in this study. This is most likely explained by the fact that patients who require a segmental resection have more advanced disease, despite the fact that the multivariable analyses adjusted for several patient and histopathological characteristics. The question whether a wedge rather than segmental resection produces improved outcome in otherwise identical patients is a topic for further research.

Tumour invasion in the resected vein was observed in 61 per cent of patients with venous resection, which is within range of reported literature (32-82 per cent).[37] It is difficult for a surgeon to distinguish tumour from peritumour al inflammation and fibrosis on a scale of millimetres. Several studies have shown varying results regarding the significance of circumference and length of vein involvement on preoperative imaging.[38, 39] The added value of intraoperative ultrasound for this assessment is being investigated within the DPCG. A previous study showed that a radical venous resection can rarely be achieved due to the microanatomy at the venous margin and the broadly invasive growth pattern of pancreatic cancer.[40] More research is needed to identify the patients who truly benefit from a venous resection, so that patients are not put at unnecessary risk for surgical complications.

In this cohort, only 8 per cent of patients received neoadjuvant therapy. This is comparable with recently published results from Germany (5 per cent) and Sweden (3 per cent), though lower than in the United Stated (28 per cent).[41] This is probably due to the fact that neoadjuvant therapy was mainly administered in a trial setting during the study period in most European countries (including the Netherlands). The comparable overall survival of the categories of venous resection after neoadjuvant therapy may be explained by the effect of the neoadjuvant therapy as well as the patient selection which occurs, as patients with advanced, aggressive or therapy-resistant tumours are no longer considered good candidates for resection. Patients who received neoadjuvant therapy with segmental resection had a very high rate of major morbidity and postoperative mortality. There is little evidence on outcomes of venous resection after neoadjuvant therapy. A previous study showed major morbidity in 7 out of 15 (47 per cent) patients who underwent venous resection after neoadjuvant therapy for locally advanced pancreatic cancer. It should be noted that these resections were performed in a high volume centre.[42]

This study has several limitations. First, with a retrospective study, collecting and interpreting data from medical records has the risk of information and classification bias. However, a previous study of the DPCA showed that data registration is complete and of high accuracy.[15] Multiple imputation was used to solve the problem of missing data. A sensitivity analyses with complete cases showed similar outcomes which suggests robustness of the results. Second, given the observational design of this study, confounding by indication should be considered as the surgeon's decision (e.g., selection for neoadjuvant therapy and venous resection) is made in the clinical and surgical context of the patient. Although the multivariable analyses adjusted for potential confounders, inherent differences between the categories of venous resection may partly explain the observed results and residual confounding cannot be ruled out. Furthermore, no definitive conclusions can be drawn regarding neoadjuvant therapy since the sample

size was relatively small and details of neoadjuvant therapy (type, cycles, doses, fractions etc.) were not available for analysis. Lastly, there was missing data in the pathology reports on tumour invasion in the resected vein (41 per cent). Unclear or absent marking of the specimen and pathology request forms can make it difficult for the pathologists to recognize the resected vein, especially in case of a wedge resection.[43] Within the DPCG, several initiatives have been set up to standardize pathology requests and reports. Strengths of the current study are, unlike previous studies, the nationwide design, including all Dutch centres performing pancreatic surgery, leading to a large cohort of patients spanning a relatively short study period (2013-2017).

In conclusion, patients who underwent venous segment resection, and not venous wedge resection, showed more major morbidity and worse overall survival. In the patients who received neoadjuvant therapy, overall survival was markedly higher and showed no difference between the categories of venous resection, whereas major morbidity and postoperative mortality rates remained high after venous segment resection. The results of this study urge the need to improve outcomes in patients who require a venous segment resection.

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SUPPLEMENTARY

Table S1. Multivariable analysis of 745 patients for major morbidity (Clavien-Dindo grade ≥III) and 952 patients for overall survival by category of venous resection with complete cases without multiple imputation

		Major morbidity			Overall survival		
		Odds ratio	95 per cent CI	P-value	Hazard ratio	95 per cent CI	P-value
Category of venous resection[a]	**Wedge resection**	0.84	0.49-1.44	0.52	0.97	0.77-1.23	0.83
	Segmental resection	2.11	1.11-3.99	0.022	1.35	1.02-1.77	0.035
Sex[b]	**Female**	1.07	0.73-1.56	0.73	1.05	0.88-1.25	0.60
Age (years)[c]		1.00	0.98-1.02	0.71	1.02	1.01-1.03	<0.001
BMI (kg/m²)[c]		1.01	0.96-1.05	0.77	0.99	0.97-1.01	0.24
ECOG[d]	**2-4**	0.88	0.48-1.62	0.68	0.95	0.72-1.27	0.73
Preoperative biliary drainage[a]		0.71	0.49-1.03	0.07	-	-	-
Preoperative resectability status[e]	**Borderline resectable**	0.74	0.45-1.21	0.22			
	Locally advanced	0.23	0.08-0.63	0.004			
Neoadjuvant therapy[a]		1.80	0.94-3.45	0.07	1.02	0.71-1.45	0.92
ASA score[f]	**III-IV**	2.14	1.41-3.24	<0.001	1.38	1.13-1.70	0.002
Minimally invasive procedure[a]		1.55	0.83-2.90	0.17	-	-	-
Arterial resection[a]		2.51	0.67-9.39	0.17	-	-	-
Additional resection[a]		2.14	1.07-4.31	0.032	-	-	-
Texture pancreatic remnant[g]	**Fibrotic/Hard**	0.85	0.58-1.25	0.42	-	-	-
Pancreatic duct diameter (mm)[c]		0.94	0.90-1.00	0.022	-	-	-
Duration of surgery (min)[c]		1.00	1.00-1.00	0.26	-	-	-
Blood loss (mL)[c]		1.00	1.00-1.00	<0.001	-	-	-
Resection margin status[h]	**R1**	-	-	-	1.30	1.09-1.56	0.004
Tumour size on pathology (mm)[c]		-	-	-	1.01	1.00-1.02	0.039
pN-stage[i]	**N1**	-	-	-	1.18	0.94-1.50	0.16
	N2	-	-	-	1.55	1.21-2.00	0.001
pM-stage[j]	**M1**	-	-	-	1.49	0.91-2.46	0.12
Tumour differentiation grade[k]	**Moderate**	-	-	-	1.74	1.26-2.41	0.001
	Poor/ Undifferentiated	-	-	-	2.47	1.76-3.46	<0.001
Lymphangio invasion[a]		-	-	-	1.10	0.92-1.33	0.31
Perineural invasion[a]		-	-	-	1.22	0.93-1.60	0.16

Table S1. Continued

CI: confidence interval; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists.

[a] Reference category: 'Without/No'
[b] Reference category: 'Male'
[c] Continuous variable
[d] Reference category: '0-1'
[e] Reference category: 'Resectable'
[f] Reference category: 'I-II'
[g] Reference category: 'Normal/soft'
[h] Reference category: 'R0'
[i] Reference category: 'N0'
[j] Reference category: 'M0'
[k] Reference category: 'Good'

Table S2. Multivariable analysis of overall survival by category of venous resection in 1252 patients without postoperative mortality and inclusion of adjuvant therapy as additional factor in the model as compared to Table 2

		Overall survival		
		Hazard ratio	**95 per cent CI**	***P*-value**
Category of venous resection[a]	*Wedge resection*	1.11	0.91-1.36	0.31
	Segmental resection	1.34	1.04-1.72	0.026
Sex[b]	*Female*	1.03	0.88-1.20	0.71
Age (years)[c]		1.01	1.00-1.02	0.12
BMI (kg/m²)[c]		0.99	0.97-1.00	0.13
ECOG[d]	*2-4*	0.84	0.65-1.08	0.17
Neoadjuvant therapy[a]		0.83	0.60-1.14	0.25
ASA score[e]	*III-IV*	1.35	1.12-1.62	0.002
Resection margin status[f]	*R1*	1.22	1.04-1.44	0.017
Tumour size on pathology (mm)[c]		1.01	1.00-1.02	0.002
pN-stage[g]	*N1*	1.12	0.91-1.38	0.28
	N2	1.54	1.23-1.92	<0.001
pM-stage[h]	*M1*	0.90	0.55-1.46	0.67
Tumour differentiation grade[i]	*Moderate*	1.57	1.18-2.09	0.002
	Poor/Undifferentiated	2.21	1.63-2.98	<0.001
Lymphangio invasion[a]		1.03	0.86-1.25	0.73
Perineural invasion[a]		1.35	1.02-1.77	0.045
Additional factor in the model as compared to Table 2				
Adjuvant therapy[a]		0.57	0.49-0.68	<0.001

CI: confidence interval; BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists.

[a] Reference category: 'Without/No'
[b] Reference category: 'Male'
[c] Continuous variable
[d] Reference category: '0-1'
[e] Reference category: 'I-II'
[f] Reference category: 'R0'
[g] Reference category: 'N0'
[h] Reference category: 'M0'
[i] Reference category: 'Good'

Table S3. Indications for relaparotomy in 23 patients with venous segment resection

Patient	Postoperative day(s)	Indication(s)
1	0	Thrombosis of venous reconstruction
2	0	Thrombosis of venous reconstruction
3	0	Thrombosis of venous reconstruction
4	0	Haemorrhage of venous reconstruction
5	0	Haemorrhage of venous reconstruction
6	0; 0	Haemorrhage (diffuse); thrombosis of venous reconstruction
7	0	Jejunal ischemia
8	1	Haemorrhage (unknown origin)
9	1	Presumed haemorrhage of venous reconstruction
10	1; 14	Presumed haemorrhage of venous reconstruction; pancreatic fistula
11	1	Thrombosis of venous reconstruction
12	1	Thrombosis of venous reconstruction
13	1	Presumed thrombosis of venous reconstruction
14	2	Thrombosis of venous reconstruction
15	4; 5, 7, 11	Thrombosis of venous reconstruction; relook; thrombosis of venous reconstruction; leakage gastroenterostomy
16	8; 22	Haemorrhage (diffuse); leakage of gastroenterostomy
17	8	Gossypiboma (instrument)
18	10	Gossypiboma (drain)
19	12	Thrombosis of venous reconstruction
20	12	Haemorrhage of venous reconstruction
21	13	Haemorrhage (laparotomy wound)
22	15	Pancreatic fistula
23	15	Leakage of gastroenterostomy

Table S4. Baseline, postoperative and histopathological characteristics by category of venous resection in 101 patients who received neoadjuvant therapy

		Without venous resection	Wedge resection	Segmental resection	*P*-value
Total		57 (56.4)	21 (20.8)	23 (22.8)	-
Baseline characteristics					
Sex	**Male**	37 (64.9)	13 (61.9)	12 (52.2)	0.57
	Female	20 (35.1)	8 (38.1)	11 (47.8)	
Age in years, median (IQR)		64 (57-71)	64 (61-69)	64 (58-71)	0.83
BMI in kg/m², mean (SD)		24.9 (3.5)	25.5 (2.2)	23.7 (3.0)	0.13
ECOG	**0-1**	55 (96.5)	20 (95.2)	22 (95.7)	0.96
	2-4	2 (3.5)	1 (4.8)	1 (4.3)	
Preoperative resectability status	**Resectable**	26 (48.1)	10 (47.6)	6 (26.1)	0.06
	Borderline resectable	14 (25.9)	4 (19.0)	13 (56.5)	
	Locally advanced	14 (25.9)	7 (33.3)	4 (17.4)	
Type of neoadjuvant therapy	**Chemoradiotherapy**	33 (57.9[a])	12 (57.1[a])	13 (56.5[a])	0.99
	Chemotherapy	24 (42.1[a])	9 (42.9[a])	10 (43.5[a])	
ASA score	**I-II**	47 (82.5)	19 (90.5)	17 (73.9)	0.36
	III-IV	10 (17.5)	2 (9.5)	6 (26.1)	
Texture pancreatic remnant	**Normal/Soft**	19 (29.8)	8 (38.1)	3 (13.0)	0.20
	Fibrotic/Hard	38 (66.7)	13 (61.9)	20 (87.0)	
Pancreatic duct in mm, median (IQR)		6 (4-9)	7 (3-10)	7 (4-9)	0.94
Blood loss during surgery in mL, median (IQR)		600 (300-1100)	900 (525-1300)	1276 (600-1466)	0.025
Postoperative characteristics					
Major morbidity (Clavien-Dindo grade ≥III)		12 (21.1)	4 (19.0)	12 (52.2)	0.012
Postoperative mortality		4 (7.0)	0	4 (17.4)	0.10
PV-SMV thrombosis		1 (1.8)	1 (4.8)	6 (26.1)	0.001
Histopathological characteristics					
Resection margins status	**R0**	38 (66.7)	13 (61.9)	16 (69.6)	0.86
	R1	19 (33.3)	8 (38.1)	7 (30.4)	
Tumour invasion in resected vein		-	1 (9.1)	5 (41.7)	-
	Missing		10	8	
Tumour size on pathology in mm, median (IQR)		26 (20-33)	27 (22-35)	31 (24-37)	0.16
pN-stage	**N0**	34 (59.6)	10 (47.6)	12 (52.2)	0.71
	N1	20 (35.1)	8 (38.1)	9 (39.1)	
	N2	3 (5.3)	3 (14.3)	2 (8.7)	

Table S4. Continued

M-stage	**M0**	54 (94.7)	21 (100)	23 (100)	0.30
	M1	3 (5.2)	0	0	
Tumour differentiation grade	**Good**	8 (14.0)	5 (23.8)	4 (17.4)	0.78
	Moderate	34 (59.6)	12 (57.1)	14 (60.9)	
	Poor/Undiff.	15(26.3)	4 (19.0)	5 (21.7)	
Lymphangio invasion		22 (38.6)	5 (26.3)	8 (42.1)	0.49
Perineural invasion		33 (57.9)	11 (57.9)	12 (63.2)	0.95

IQR: inter quartile range; BMI: body mass index; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; PV-SMV: portal vein-superior mesenteric vein
Values are frequencies (per cent) unless indicated otherwise
[a] Percentage is based on the number of patients who received neoadjuvant therapy

Table S5. Multivariable analysis of major morbidity (Clavien-Dindo ≥III) and overall survival by category of venous resection in 101 patients who received neoadjuvant therapy

		Major morbidity			Overall survival		
		Odds ratio	95 per cent CI	*P*-value	Hazard ratio	95 per cent CI	*P*-value
Category of venous resection[a]	**Wedge resection**	0.84	0.23-3.10	0.80	1.16	0.53-2.51	0.72
	Segmental resection	3.75	1.26-11.17	0.018	1.21	0.55-2.27	0.63
Age (years)[b]		-	-	-	1.04	0.98-1.09	0.07
ASA score[c]	**III-IV**	1.05	0.30-3.66	0.94	1.70	0.75-3.84	0.21
Pancreatic duct diameter (mm)[b]		0.96	0.81-1.12	0.58	-	-	-
Blood loss (mL)[b]		1.00	1.00-1.00	0.045	-	-	-
Resection margin status[d]	**R1**	-	-	-	2.05	1.03-4.09	0.041
Tumour size on pathology (mm)[b]		-	-	-	1.00	0.97-1.02	0.74
pN-stage[e]	**N1**	-	-	-	1.27	0.62-2.59	0.51
	N2	-	-	-	2.09	0.75-5.85	0.16
Tumour differentiation grade[f]	**Moderate**	-	-	-	1.78	0.60-5.27	0.30
	Poor/Undifferentiated	-	-	-	3.30	0.95-11.42	0.06
Lymphangio invasion[a]		-	-	-	0.63	0.28-1.43	0.27
Perineural invasion[a]		-	-	-	0.99	0.44-2.22	0.97

CI: confidence interval; ASA: American Society of Anesthesiologists

[a] Reference category: 'Without/No'

[b] Continuous variable

[c] Reference category: 'I-II'

[d] Reference category: 'R0'

[e] Reference category: 'N0'

[f] Reference category: 'Good'

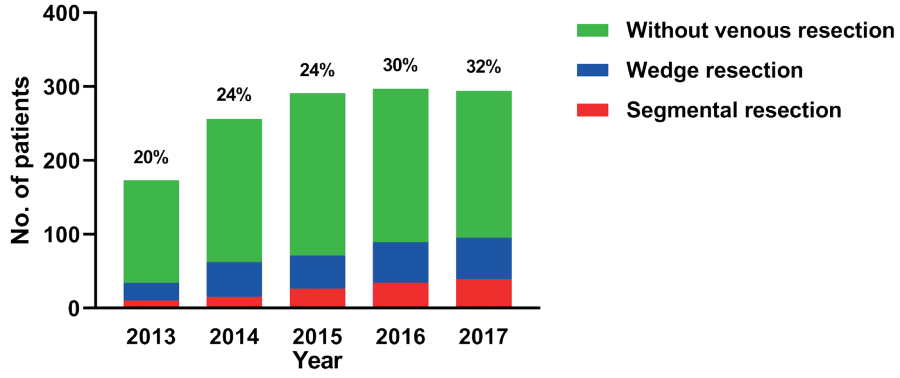


Figure S1. Pancreatoduodenectomies performed with and without venous resection over the study period

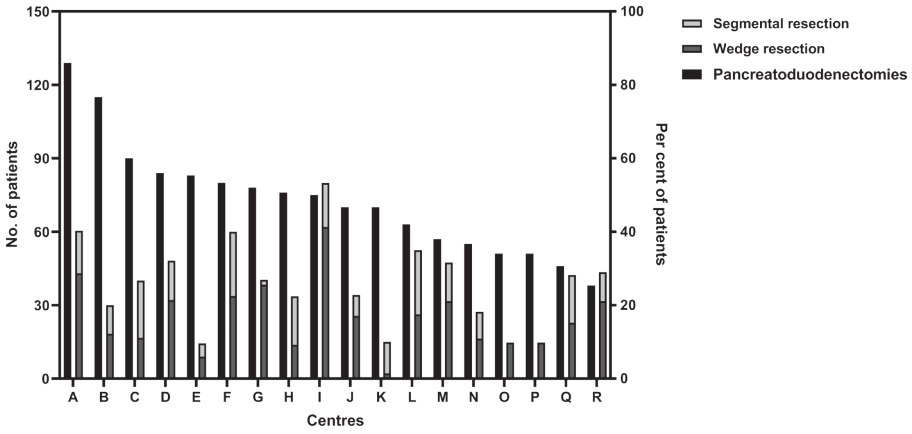
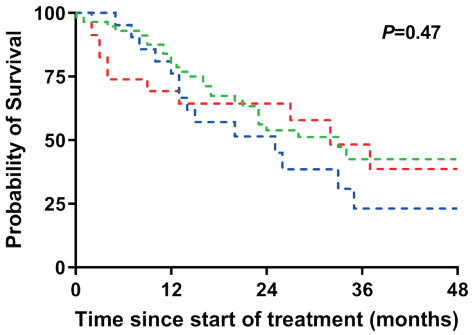


Figure S2. No. of pancreatoduodenectomies (plotted at left y-axis) and per cent of venous wedge and segment resection (plotted at right y-axis) for pancreatic cancer per centre performed over the study period



Numbers at risk					
Without venous resection	57	46	23	8	1
Wedge resection	21	16	8	2	0
Segmental resection	23	14	10	5	1

Figure S3. Kaplan-Meier curves of overall survival after pancreatoduodenectomy for pancreatic cancer by category of venous resection in 101 patients who received neoadjuvant therapy

Author response to comment on: Venous wedge and segment resection during pancreatoduodenectomy for pancreatic cancer: impact on short- and long-term outcomes in a nationwide cohort analysis

J.V. Groen, N. Michiels, J.S.D. Mieog

Br J Surg. 2022 Jun 14;109(7):e88. doi: 10.1093/bjs/znac060. PMID: 35416240.

To the Editor

We appreciate the interest of Wang et al. in our study[1] in which we analysed the results of venous resection during pancreatectomy in a nationwide cohort. We address the comments from Wang et al. point-by-point below.

First, Wang and colleagues comment on our inclusion of patients with M1 stage. We agree that there is currently no evidence to support performing pancreatic resection in patients with metastasized pancreatic cancer. However, some patients who are cM0 staged at clinical staging and subsequently undergo resection are in fact pM1 staged at pathological staging. In our study we purposely also included patients who underwent pancreatoduodenectomy and were only thereafter pM1 staged (2.5%), because we aimed to investigate current clinical practice. A post-hoc subgroup analysis of only patients who were pM0 staged after pancreatoduodenectomy, showed similar results of worse overall survival in patients with segmental venous resection (hazard ratio 1.44, 97% confidence interval 1.13-1.84).

Second, Wang and colleagues suggest that the lower rate of adjuvant therapy in the segmental venous resection group explains the lower overall survival. We like to point to our analysis provided in Table S2 in which we investigated the use of adjuvant therapy in patients without postoperative mortality. In this multivariable analysis, patients with segmental venous resection still showed worse overall survival (hazard ratio 1.34 95% confidence interval 1.04-1.72) and, not surprisingly, patients who received adjuvant therapy showed better overall survival (hazard ratio 0.57, 97% confidence interval 0.49-0.68). Of note, confounding by indication should be considered when interpreting the results of observational data as the decision to use adjuvant therapy was made in the clinical context of the patient. Therefore, we chose to only publish these results in the Supplementary Material.

Lastly, Wang and colleagues comment on our non-inclusion of resection margin status in the multivariable analysis, where we in fact did include resection margin status as factor in the multivariable analysis for overall survival provided in Table 2. The suggested "inferior mesenteric vein approach" by the Wang's team might be an interesting

approach to improve radicality. Even more so, we would like to stress the importance of including neoadjuvant chemotherapy in the treatment strategy for patients with a need for venous resection to improve radicality. In addition, improvements in pre- and intraoperative imaging tools can also help to better direct the performance of a radical venous resection. We are currently analysing the data of our ULTRAPANC study which assesses the added value of intraoperative ultrasound in patients with pancreatic cancer and vascular involvement (https://www.trialregister.nl/trial/7621).

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CHAPTER 7

Practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer: a nationwide cohort study

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Submitted

ABSTRACT

Background: Practice variation exists in venous resection during pancreatoduodenectomy but little is known about the potential causes and consequences as large studies are lacking. This study explores the potential causes and consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands.

Methods: This nationwide retrospective cohort study included patients undergoing pancreatoduodenectomy for pancreatic cancer in 18 centers from 2013 through 2017.

Results: Among 1311 patients undergoing pancreatoduodenectomy, 351 (27%) had a venous resection and the overall median annual center volume of venous resection was 4. No association was found between center volume of pancreatoduodenectomy and the rate of venous resections, nor between patient and tumor characteristics and the rate of venous resections per center. Female sex, lower BMI, neoadjuvant therapy, venous involvement and stenosis on imaging were predictive for venous resection. Adjusted for these factors, three centers performed significantly more and three center performed significantly less venous resections than expected. In patients with venous resection, significantly less major morbidity (22% vs 38%) and longer overall survival (median 16 vs 12 months) was observed in centers with an above median annual volume of venous resections (>4).

Conclusions: Significant practice variation between centers in the Netherlands in venous resection during pancreatoduodenectomy for pancreatic cancer were not explained by patient and tumor characteristics alone. The clinical outcomes of venous resection might be related to the volume of the procedure.

INTRODUCTION

The prognosis of patients with pancreatic cancer has barely improved over the last decades.(1) Radical tumor resection with (neo)adjuvant chemo(radio)therapy remains the standard treatment.(2, 3) A partial resection of the portal or superior mesenteric vein (PV-SMV) may be required to ensure an R0 margin status.(4)

A recent international expert survey showed considerable variation in surgical management of pancreatoduodenectomy with PV-SMV involvement (hereafter: venous involvement). For example, most international experts preferred a type 3 (segmental) PV-SMV resection and reconstruction (hereafter: venous resection), whereas Dutch surgeons equally preferred type 1 (wedge) and type 3 venous resection.(5) In a nationwide study in the Netherlands, we observed that the rate of venous resection during pancreatoduodenectomy for pancreatic cancer varies considerably between centers (10-53%).(6) These variations in surgical management and rates of venous resection can be explained by anatomical, biological and conditional patient characteristics(7), however, it is unknown to what extent personal preferences and experience of the surgical team influence the rate of venous resection.(8-10)

In the aforementioned nationwide study, we found that rates of major morbidity and PV-SMV thrombosis and overall survival of patients undergoing venous segment resection in the Netherlands are worse compared with results reported in other recent literature.(6, 8-10) To improve outcomes for patients with pancreatic cancer with venous involvement we need to have better insight in the associated factors, concerning surgical procedure as well as patient and center characteristics. It has been suggested that venous resection during pancreatic surgery should be performed only at high-volume center with experienced surgical and multidisciplinary teams.(4, 11) Volume–outcome relationships in pancreatic surgery in the Netherlands has already been proven and showed the benefits of nationwide centralization within the Dutch Pancreatic Cancer Group (DPCG).(12-14) To date there are no nationwide studies available that investigate the variety of rate of venous resection per center after correction for patient and tumor characteristics and the association between clinical outcomes and the volume or rate of venous resections during pancreatoduodenectomy performed at a center.

The aim of this study was to explore the potential causes and consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands.

METHODS

Study design and patient selection

The cohort included all 18 centers of the multidisciplinary DPCG, each performing at least 20 pancreatoduodenectomies per year.(15) Patients after pancreatoduodenectomy for pancreatic adenocarcinoma (postoperative pathological diagnosis, hereafter: pancreatic cancer) from 2013 through 2017 registered in the mandatory, prospective, nationwide Dutch Pancreatic Cancer Audit (DPCA)(16) were included. All patients are discussed at a pancreatic multidisciplinary team meeting as mandatory by the national quality audit. A waiver for informed consent was issued by the Medical Ethics Committee of the Leiden University Medical Centre (G18.103) due to the retrospective design. The study is reported in accordance with the STROBE criteria.(17)

Data collection

Data were obtained from the DPCA and included baseline, intraoperative, postoperative, and histopathological characteristics. Additional data were manually extracted from the patients' medical records (e.g., category of venous resection, blood loss, duration of surgery, follow-up characteristics).

Definitions

Carcinoembryonic antigen (CEA) and Carbohydrate Antigen 19-9 (CA 19-9) were scored as highest preoperative values and previously published cut-off values were used for categorization.(18) Resectability criteria were defined according to the DPCG criteria: no arterial involvement and venous involvement ≤90° was considered resectable; arterial involvement ≤90° and/or venous involvement 91°-270° without occlusion was considered borderline resectable, arterial involvement >90° and/or venous involvement >270° or occlusion was considered locally advanced. Neoadjuvant therapy was categorized as no/yes (mainly gemcitabine-based chemoradiotherapy in the PREOPANC trial(19)). Venous involvement on preoperative imaging was defined as absence of a fat plane between the tumor and PV-SMV and was categorized as ≤90°/>90°. PV-SMV occlusion or stenosis (hereafter: venous stenosis) on preoperative imaging was defined as luminal narrowing/wall deformity of the PV-SMV and was categorized as no/yes. Type of venous resection was classified according to the International Study Group of Pancreatic Surgery (ISGPS) guidelines(4) and reported by wedge (Type 1 and 2) or segmental (Type 3 and 4) resection. Additional resection was defined as any additional resection not including standard pancreatoduodenectomy.(20) Postoperative PV-SMV thrombosis within 30 days following surgery was scored based on imaging studies which were performed at discretion of the attending physician. The Clavien-Dindo classification was scored within 30 days following surgery and grade ≥III was considered as major morbidity.(21) Postoperative mortality was defined as death within 90 days following surgery, unless

the cause of death was clearly disease-related (e.g., early recurrence or metastasis) and not surgery-related.(22) The overall median annual center volume of venous resection during the study period was determined to analyze outcomes. Centers were classified as "above median" when the median annual volume of venous resections was above the overall median annual volume and "below median" when the median annual volume of venous resections was below the overall median annual volume of venous resections. The eighth edition of the TNM classification was used for histological classification.(23) An R1 resection margin was defined as the presence of tumor cells within 1 mm of the resection margin.(24) Due to the inclusion of patients with neoadjuvant therapy, overall survival was calculated as the time in months between the start of treatment (day of surgery or start of neoadjuvant therapy) and the date of death (or last follow-up visit) and was truncated at 48 months.

Main outcome and comparison

The main outcomes of this study were (type of) venous resection, postoperative PV-SMV thrombosis, postoperative mortality, postoperative major morbidity and overall survival. Patients were analyzed by venous resection (no vs yes), type of venous resection (venous wedge vs segment resection), individual center (1 to 18) and annual center volume of venous resections during the study period (above median vs below median [median >4 vs ≤4]). Sensitivity analysis were performed with other thresholds of median annual center volume of venous resections.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A two-sided P-value <0.05 was considered statistically significant. Missing data were imputed 25 times based on relevant variables. Log-transformation was performed for not-normally distributed variables.(25) Continuous variables were presented as median with interquartile range (IQR) and compared using the Kruskal-Wallis test. Categorical variables were presented as frequencies with percentages and compared using the chi-square test or Fisher's exact test. Overall survival was reported as the median with 95% confidence interval (CI), and Kaplan-Meier curves and log-rank tests were used to compare groups. Linear regression analysis was performed to assess the relationship between (type of) venous resection and several patient and tumor characteristics per center.

Univariable binary logistic regression analysis was performed to identify preoperative predictive factors for (type of) venous resection. Center variation in (type of) venous resection was assessed using observed/expected ratios adjusted for the identified preoperative predictive factors (analysis in R version 4.1.0 (R Core Team, 2021). The observed/expected ratio indicates if a center performed more (>1) or less (<1) venous

(segment) resections than expected. Statistical significance was considered if centers were outside the 95% CI.

Multivariable binary logistic regression analysis and Cox proportional hazards model were performed to assess the impact of above and below median annual volume of venous resections on postoperative PV-SMV thrombosis, mortality, major morbidity and overall survival and adjust for potential confounders.

RESULTS

Baseline characteristics

In total, 1311 patients undergoing pancreatoduodenectomy for pancreatic cancer were included, of whom 351 (27%) had a venous resection (Table 1). Preoperative and intraoperative characteristics of patients stratified for venous resection are shown in Table 1. Between the 18 centers, the total volume of pancreatoduodenectomies for pancreatic cancer during the 4-year study period varied from 38 to 129 patients and the total volume of venous resections varied from 5 to 52 patients (10-53%) with an overall median annual center volume of 4 venous resections (Figure 1). Out of 18 centers, 8 centers had an above (>4) median annual volume of venous resections with a total of 235 patients (67% of all venous resections).

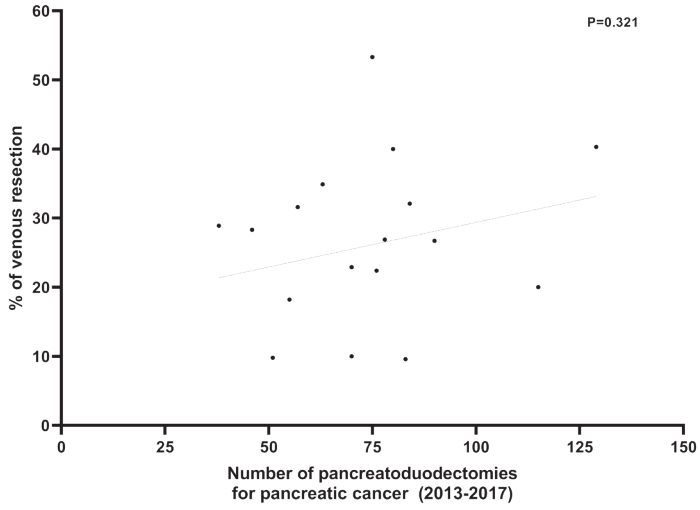

Figure 1. Relationship between center volume and rate of venous resections

Practice variation among centers with regards to performing venous resection

There was no relationship between center volume of pancreatoduodenectomy and the rate of venous resections (Figure 1). There was no relationship between anatomical (tumor diameter, venous involvement and venous stenosis on imaging), biological (CEA, CA19-9, lymphadenopathy on imaging) and conditional patient characteristics (sex, age, ASA score) and the rate of venous resections per center (Figure S1). In univariable analysis, female sex, lower BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging were predictive factors for venous resection. Adjusted for these factors, three centers performed significantly more and three centers performed significantly less venous resections than predicted (Figure 2).

The rate of venous segment resection (vs wedge resection) varied from 0-86% between centers and there was no relationship between rate of venous resections, anatomical, biological and conditional patient characteristics and rate of venous segment resection per center (Figure S2). In univariable analysis, neoadjuvant therapy and venous involvement on imaging were predictive factors for venous segment resection. Adjusted for these factors, three centers performed significantly less venous segment resections than expected (Figure S3).

Table 1. Baseline characteristics of patients stratified for venous resection

		Venous resection				
		No		Yes		
		N	%	N	%	P-value
Total		960	73.2	351	26.8	-
Preoperative characteristics						
Sex	**Male**	554	57.7	180	51.3	0.038
	Female	406	42.3	171	48.7	
Age (years), median (IQR)		68 (61-74)		68 (61-74)		0.747
BMI (kg/m²), median (IQR)		25.1 (4.2)		24.3 (3.7)		0.008
ECOG	**0-1**	858	89.7	306	87.7	0.286
	2-4	98	10.3	43	12.3	
ASA	**I-II**	742	77.3	273	77.8	0.852
	III-IV	218	22.7	78	22.2	
Preoperative weight loss (%), median (IQR)		9 (6-13)		10 (6-14)		0.170
CEA (ug/L), median (IQR)		3.4 (2.2-5.8)		4.3 (2.3-5.8)		0.099
CA19-9 (kU/L), median (IQR)		94 (21-298)		140 (32-512)		0.024
Preoperative biliary drainage		542	56.5	203	57.8	0.656
Neoadjuvant therapy		57	5.9	44	12.5	<0.001

Table 1. Continued

Neoadjuvant therapy*	**Chemo-radiotherapy**	33	3.4	25	7.1	>0.999
	Chemotherapy	24	2.5	19	5.4	
Tumor diameter on imaging (mm), median (IQR)		25 (19-31)		27 (20-33)		0.008
Venous involvement on imaging	**≤90**	827	86.2	189	53.8	<0.001
	>90	133	13.9	162	46.2	
Venous stenosis on imaging		55	5.8	60	18.6	<0.001
Lymphadenopathy on imaging		147	15.3	56	16.0	0.796
Preoperative resectability status**	**Resectable**	781	83.4	174	50.4	<0.001
	Borderline resectable	113	12.1	139	40.3	
	Locally advanced	43	4.6	32	9.3	
Intraoperative characteristics						
Type of surgery	**Classical Whipple**	347	36.1	128	36.5	0.832
	PPPD	591	61.6	213	60.7	
	PRPD	22	2.3	10	2.8	
Minimally invasive procedure		109	11.4	14	4.0	<0.001
Type of venous resection***	**Type 1**	-		197	56.1	-
	Type 2			30	8.5	
	Type 3			97	27.6	
	Type 4	-		27	7.7	
Arterial resection		9	0.9	8	2.3	0.057
Additional resection		51	5.3	22	6.3	0.504
Duration of surgery (min), median (IQR)		295 (239-377)		360 (290-437)		<0.001
Blood loss during surgery (mL), median (IQR)		600 (350-1000)		800 (500-1466)		<0.001
Postoperative characteristics						
Postoperative PV-SMV thrombosis		9	0.9	34	9.7	<0.001
Postoperative mortality		41	4.3	18	5.1	0.507
Postoperative major morbidity		224	23.3	94	26.8	0.197
Adjuvant therapy		647	68.2	236	67.7	0.830

*Patients who received neoadjuvant therapy
** According to the Dutch Pancreatic Cancer Group criteria
*** According to the International Study Group of Pancreatic Surgery criteria

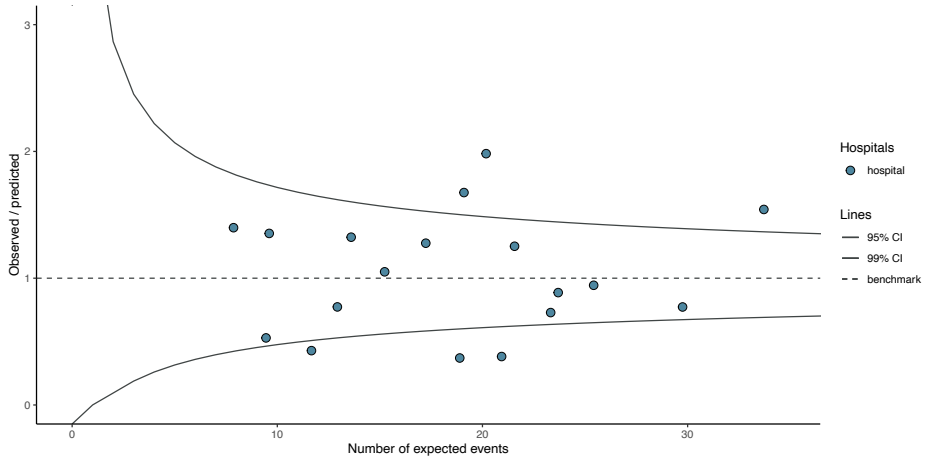

Figure 2. Funnel plot of adjusted center practice variation in the use of venous resection during pancreatoduodenectomy for pancreatic cancer (adjusted for sex, BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging)

Practice variation regarding volume of venous resection and postoperative outcomes

There was no linear relationship between volume or rate of venous resections per center and postoperative PV-SMV thrombosis, mortality and major morbidity (Figure 3).

Preoperative, intraoperative, postoperative and histopathological characteristics stratified for above (>4) and below (≤4) median annual center volume of venous resections are shown in Table 2. Patients with venous resection in centers with an above median annual volume of venous resections had less blood loss during surgery (P=0.001), underwent less often a venous segment resection (32% vs 43%, P=0.032) and had less often lymphangio invasion (57% vs 73%; P=0.007). Other preoperative, intraoperative, postoperative and histopathological (e.g. resection margin status) characteristics were not different between above and below median annual center volume of venous resections. Patients with venous resection in centers with an above median annual volume of venous resections showed less postoperative PV-SMV thrombosis (6% vs 17%, P=0.001), mortality (2% vs 11%, P<0.001), and major morbidity (22% vs 38%, P=0.001), had less often lymphangio-invasion (57% vs 73%, P=0.007), and longer overall survival (median 16 vs 12 months, P<0.001) (Figure 4). An analysis of overall survival in patients without postoperative mortality showed a similar difference (median 17 months vs 13 months, P=0.009) (Figure S4).

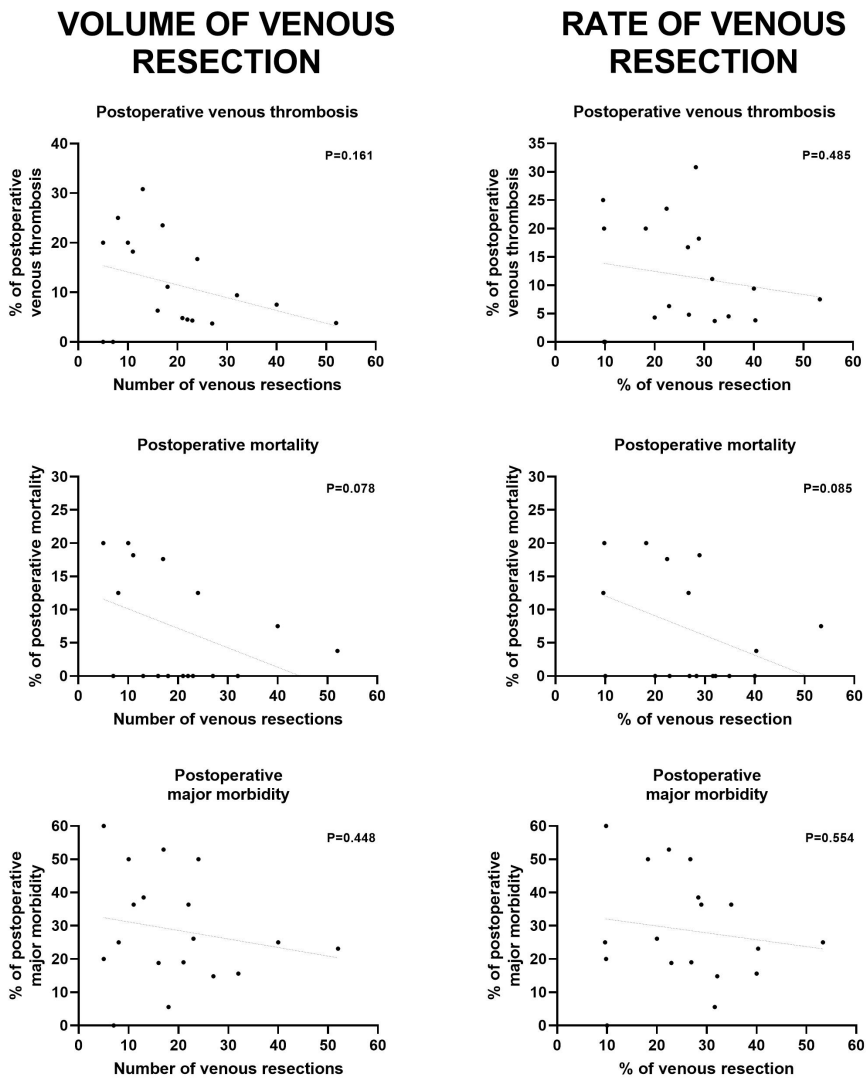

Figure 3. Relationship between volume (left column) and rate (right column) of venous resections and postoperative outcomes

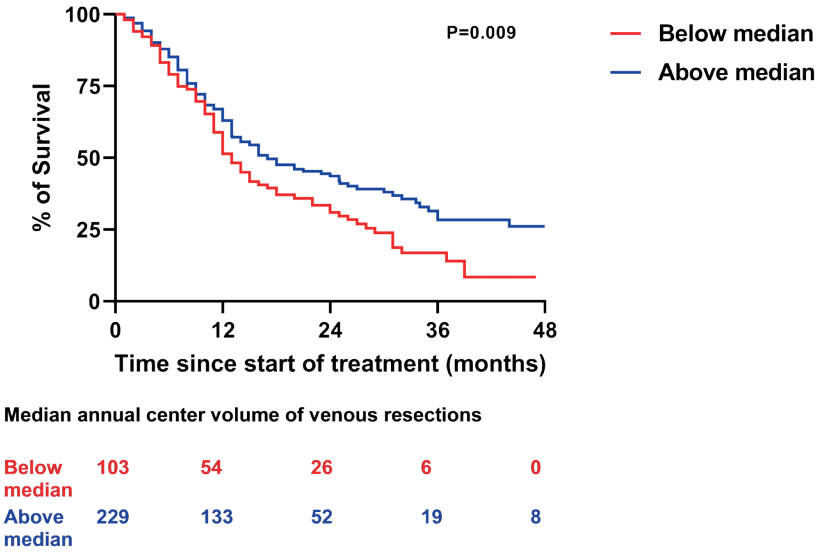

Figure 4. Kaplan–Meier curves of overall survival after start of treatment (day of surgery or start of neoadjuvant therapy) for pancreatic cancer stratified for median annual center volume of venous resections (below: ≤4; above: >4 venous resections)

Table 2. Baseline, postoperative and histopathological characteristics of patients with venous resection stratified for median annual center volume of venous resections

		Median annual center volume of venous resections				
		Below (≤4)		Above (>4)		
		N	%	N	%	P-value
Total		116	33.0	235	67.0	-
Preoperative characteristics						
Sex	**Male**	53	45.7	127	54.0	0.141
	Female	63	54.3	108	46.0	
Age (years), median (IQR)		69 (62-74)		68 (61-73)		0.678
BMI (kg/m²), median (IQR)		24.1 (22.1-26.6)		23.8 (21.7-26.0)		0.229
ECOG*	**0-1**	105	90.5	201	86.3	0.255
	2-4	11	9.5	32	13.7	
ASA	**I-II**	88	75.9	185	78.7	0.544
	III-IV	28	24.1	50	21.3	
Preoperative biliary drainage		64	55.2	139	59.1	0.478
Neoadjuvant therapy		13	11.2	31	13.2	0.597
Preoperative resectability* status	**Resectable**	60	53.1	114	49.1	0.788

Table 2. Continued

	Borderline resectable	43	38.1	96	41.4	
	Locally advanced	10	8.8	22	9.5	
Intraoperative characteristics						
Texture pancreatic remnant	**Normal/Soft**	35	33.3	71	33.8	0.933
	Fibrotic/Hard	70	66.7	139	66.2	
Pancreatic duct diameter in mm, median (IQR)		7 (4-10)		6-4-9)		0.465
Blood loss during surgery in mL, median (IQR)		1000 (600-1750)		700 (450-1200)		0.001
Type of venous resection**	**Type 1**	58	50.0	139	59.1	0.142
	Type 2	8	6.9	22	9.4	
	Type 3	41	35.3	56	23.8	
	Type 4	9	7.8	18	7.7	
Postoperative characteristics						
Postoperative PV-SMV thrombosis		20	17.2	14	6.0	0.001
Postoperative mortality		13	11.2	5	2.1	<0.001
Postoperative major morbidity		44	37.9	50	21.3	0.001
Adjuvant therapy		69	60.0	167	71.4	0.033
Histopathological characteristics						
Resection margins status	**R0**	38	32.8	86	36.6	0.479
	R1	78	67.2	149	63.4	
Tumour size on pathology in mm, median (IQR)		32 (25-40)		34 (25-40)		0.816
pN-stage	**N0**	29	25.0	64	27.2	0.898
	N1	46	39.7	89	37.9	
	N2	41	35.3	82	34.9	
M-stage	**M0**	114	98.3	228	97.0	0.484
	M1	2	1.7	7	3.0	
Tumour differentiation grade	**Good**	9	8.6	27	12.7	0.390
	Moderate	57	54.3	119	56.1	
	Poor/Undiff.	39	37.1	66	31.1	
Lymphangio invasion		75	72.8	100	56.5	0.007
Perineural invasion		92	87.6	187	90.8	0.386

* According to the Dutch Pancreatic Cancer Group criteria
** According to the International Study Group of Pancreatic Surgery criteria

Table 3. Multivariable analysis for postoperative major morbidity (Clavien-Dindo grade ≥III) and overall survival (since start of treatment) in patients with venous resection

Postoperative major morbidity		Odds ratio	95% CI		P-value
Median annual center volume of venous resections	**Below (≤4)**	Reference			
	Above (>4)	0.447	0.235	0.852	0.014
Type of venous resection	**Wedge**	Reference			
	Segment	2.278	1.178	4.408	0.014
Sex	**Male**	Reference			
	Female	1.903	1.004	3.608	0.049
Age (years)		0.993	0.959	1.028	0.681
BMI (kg/m²)		0.966	0.884	1.055	0.440
ASA score	**I-II**	Reference			
	III-IV	2.399	1.201	4.795	0.013
Preoperative biliary drainage	**No**	Reference			
	Yes	1.337	0.710	2.516	0.368
Neoadjuvant therapy	**No**	Reference			
	Yes	1.633	0.649	4.108	0.297
Pancreatic duct diameter (mm)		0.928	0.847	1.016	0.106
Texture pancreatic remnant	**Normal/soft**	Reference			
	Fibrotic/Hard	0.935	0.482	1.814	0.842
Blood loss during surgery (mL)		1.000	1.000	1.000	0.133

Overall survival		Hazard ratio	95% CI		P-value
Median annual center volume of venous resections	**Below (≤4)**	Reference			
	Above (>4)	0.678	0.502	0.917	0.012
Type of venous resection	**Wedge**	Reference			
	Segment	1.305	0.967	1.761	0.081
Sex	**Male**	Reference			
	Female	1.087	0.801	1.474	0.594
Age (years)		1.012	0.996	1.030	0.150
BMI (kg/m²)		0.976	0.934	1.021	0.289
ASA score	**I-II**	Reference			
	III-IV	1.637	1.161	2.310	0.005
Neoadjuvant therapy	**No**	Reference			
	Yes	0.898	0.542	1.486	0.675
Resection margin status	**R0**	Reference			
	R1	1.509	1.085	2.098	0.015

Table 3. Continued

Tumor diameter on pathology (mm)		0.990	0.977	1.003	0.147
pN stage	**N0**	Reference			
	N1	0.909	0.625	1.322	0.617
	N2	1.255	0.853	1.847	0.249
pM stage	**M0**	Reference			
	M1	0.845	0.256	2.793	0.783
Tumor differentiation grade	**Good**	Reference			
	Moderate	1.451	0.849	2.480	0.174
	Poor/Undiff.	2.017	1.165	3.492	0.012
Lymphangio invasion	**No**	Reference			
	Yes	0.849	0.614	1.173	0.321
Perineural invasion	**No**	Reference			
	Yes	1.046	0.691	1.582	0.832

Missing values were imputed for pancreatic duct (N=76), texture pancreatic remnant (N=36), blood loss during surgery (N=32), tumor size on pathology (N=3), tumour differentiation grade (N=34), lymphangio invasion (N=71), perineural invasion (N=40)

DISCUSSION

This nationwide study of 1311 patients undergoing pancreatoduodenectomy for pancreatic cancer found relevant practice variation in venous resection and the associated outcomes between centers. The rate of venous resection per center varied from 10 to 53% with an overall annual median of 4 venous resections per center. There was no clear relationship between center pancreatoduodenectomy volume and rate or type of venous resection and between anatomical, biological and conditional patient characteristics, center characteristics and rate or type of venous resections per center. Adjusted for predictive factors (female sex, lower BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging), three centers performed significantly more and three centers performed significantly less venous resections than expected. Patients with venous resection in centers with a higher annual volume of venous resections might have less postoperative PV-SMV thrombosis, mortality, and major morbidity and longer overall survival.

The observed variation in the rate of venous resection is in line with a previous meta-analysis (6-65%).(26) In contrast with our study, this meta-analysis did not analyze the potential background and impact of this variation. The choice to perform a venous resection and reconstruction type is multifactorial and likely based on the combination of surgical teams' preference and skills and anatomy of the patient (circumference, length

and stenosis of venous involvement and tumor diameter).(27) It is noteworthy that most Dutch surgeons equally prefer a venous wedge or segment resection, but in practice far more often perform a wedge resection.(5) On patient-level in the total cohort, venous involvement was a predictive factor for venous resection. In contrast, on a hospital level, there was no linear relationship between percentage of patients with venous involvement and percentage of venous resections per center. Little is known which details motivate the decision and there are no standardized guidelines on this topic. Awareness of the observed practice variations in this study will lead to efforts identifying best practices, standardizing the approach for patients with pancreatic cancer and suspected venous involvement with the goal to improve outcomes.

Several studies have shown an increase of venous resection rate over time, indicating that there should be standardized education in the training program of pancreatic surgeons.(28, 29) It has been suggested that venous resection during pancreatic surgery should be performed only at high-volume center with experienced surgical and multidisciplinary teams.(4, 11) Patients with venous resection in centers with an above median annual volume of venous resection (>4) had significantly lower major morbidity (22% vs 38%) and longer overall survival (median 16 months vs 12 months) in this study, which remained significant in multivariable analysis. The volume-outcome relationship in pancreatic surgery has already been described and led to centralization of pancreatic surgery in the Netherlands.(12) Centralization of pancreatoduodenectomy with venous resection alone would be challenging, as not all venous resections are anticipated preoperatively.(30) In a recent international multicenter (N=24) cohort study of benchmark cases undergoing pancreatoduodenectomy with venous resection for all indications in centers performing >40 complex pancreas interventions per year, no association was found between volume of venous resection per center and the 90-day Comprehensive Complication Index®.(31) It should be noted that our nationwide study, within the centralized DPCG, included all Dutch centers performing pancreatic surgery and only included patients with pancreatic cancer. The sensitivity analysis showed favorable outcomes of median annual center volume of ≤6 vs >6 venous resections, though not for the higher threshold of ≤9 vs >9. This might be related to case-mix factors and sample size as only one hospital performed median >9 annual venous resections during the study period. Further studies are needed to define the volume-outcome relationship in pancreatoduodenectomy with venous resection and determine its possible clinical relevance.

We believe pancreatoduodenectomy with venous resection is technically challenging for the surgeon and also more challenging for the multidisciplinary team (e.g., perioperative hemodynamic monitoring and postoperative imaging and thromboprophylaxis of which we unfortunately did not have data). Therefore, multidisciplinary efforts are needed to identify best practices, and minimize unwanted practice variation among

centers in patients with pancreatic cancer and suspected venous involvement. After the results of our previous(6) and present study, we organized a hands-on workshop with an international expert faculty on surgical anatomy and perioperative techniques during venous resection in patients with pancreatic cancer for Dutch surgeons.(32). The opinions of this seminar were positive, it was regarded as a welcome addition to the regular training program of pancreatic surgeons in the Netherlands. Of course, this is a subjective outcome. An interesting topic would be whether our research on pancreatic cancer and suspected venous involvement and this seminar leads to minimalization of practice variation and standardization of the approach in the Netherlands and ultimately improve outcomes.

This study has limitations. First, due to the retrospective design and data collection, the risk of information and classification bias should be considered. This is especially true for the manually collected variables, although the available data of the DPCA has proven to be complete and of high accuracy.(16) Second, only patients with pancreatic cancer were included and possibly the results cannot be extrapolated to patients with venous resections during pancreatoduodenectomy for other indications. Also, in the Netherlands, pancreatic surgery has already been centralized within the DPCG (at least 20 pancreatoduodenectomies per year per center, 18 centers during the study period, currently 14 centers) and therefore results cannot be directly extrapolated to healthcare systems with no or other centralization methods. These different healthcare systems can adopt and standardize their approach from identified best practices. Third, changing indications from upfront resection to the increasing use of neoadjuvant therapies may have biased the results and limit the generalizability of the results (only 8% neoadjuvant therapy vs 28% in the United States(33)). The current study period (2013-2017) was chosen so that it included a limited number of patients with neoadjuvant chemotherapy (homogeneous cohort) and allowed for adequate follow-up time. Fourth, given the observational design of this study, confounding by indication should be considered as the surgical teams' decision (e.g., selection for neoadjuvant therapy and venous resection) was made in the clinical and surgical context of the patient. The results of median annual center volume of venous resection should be considered with caution as there was no linear association between clinical outcomes and absolute volume or percentage of venous resection per center, the cut-off is low and relatively arbitrary (overall median annual center volume of only four venous resections), the retrospective design of the study and therefore results might be susceptible to bias. Furthermore, the cut-off is not externally validated and are not meant as a volume standard but rather as a surrogate for a standardized approach.

In conclusion, this nationwide study showed that significant practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer between Dutch centers could not be explained solely by variations in patient and tumor characteristics. The decision to perform a venous resection is apparently also dependent on variables not available in the registry, and might be associated with characteristics and preferences of the surgical team. The clinical outcomes of venous resection might be related to the volume of the procedure.

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SUPPLEMENTAL MATERIAL

Table s1. Baseline, postoperative and histopathological characteristics of patients with venous resection stratified for median annual center volume of venous resections

		Median annual center volume of venous resections				
		Below (≤6)		Above (>6)*		
		N	%	N	%	P-value
Total		227	64.7	124	35.3	-
Preoperative characteristics						
Sex	**Male**	115	50.7	65	52.4	0.753
	Female	112	49.3	59	47.6	
Age (years), median (IQR)		68 (61-73)		69 (62-74)		0.279
BMI (kg/m²), median (IQR)		24.2 (22.2-26.5)		23.2 (21.2-25.4)		0.011
ECOG	**0-1**	206	90.7	100	82.0	0.017
	2-4	21	9.3	22	18.0	
ASA	**I-II**	179	78.9	94	75.8	0.511
	III-IV	48	21.1	30	24.2	
Preoperative biliary drainage		128	56.4	75	60.5	0.458
Neoadjuvant therapy		22	9.7	22	17.7	0.029
Preoperative resectability status**	**Resectable**	112	50.2	62	50.8	0.655
	Borderline resectable	88	39.5	51	41.8	
	Locally advanced	23	10.3	9	7.4	
Intraoperative characteristics						
Texture pancreatic remnant	**Normal/Soft**	64	31.7	42	37.2	0.323
	Fibrotic/Hard	138	68.3	71	62.8	
Pancreatic duct diameter in mm, median (IQR)		6 (4-10)		5 (4-8)		0.098
Blood loss during surgery in mL, median (IQR)		1000 (500-1700)		600 (400-1000)		<0.001
Type of venous resection* **	**Type 1**	128	56.4	69	55.6	0.063
	Type 2	13	5.7	17	13.7	
	Type 3	68	30.0	29	23.4	
	Type 4	18	7.9	9	7.3	
Postoperative characteristics						
Postoperative PV-SMV thrombosis		26	11.5	8	6.5	0.130
Postoperative mortality		13	5.7	5	4.0	0.491
Postoperative major morbidity		67	29.5	27	21.8	0.117
Overall survival (months), median (95% CI)		13 (11-15)		25 (13-37)		<0.001

Table s1. Continued

Adjuvant therapy		141	62.4	95	77.2	0.005
Histopathological characteristics						
Resection margins status	**R0**	74	32.6	50	40.3	0.148
	R1	153	67.4	74	59.7	
Tumour size on pathology in mm, median (IQR)		34 (27-40)		31 (25-40)		0.186
pN-stage	**N0**	59	26.0	34	27.4	0.921
	N1	89	39.2	46	37.1	
	N2	79	34.8	44	35.5	
M-stage	**M0**	225	99.1	117	94.4	0.007
	M1	2	0.9	7	5.6	
Tumour differentiation grade	**Good**	21	10.5	15	12.8	0.349
	Moderate	107	53.5	69	59.0	
	Poor/Undiff.	72	36.0	33	28.2	
Lymphangio invasion		121	61.7	54	64.3	0.686
Perineural invasion		190	90.0	89	89.0	0.776

* Three centers with a median annual center volume of respectively 7, 9, and 13 venous resections

** According to the Dutch Pancreatic Cancer Group criteria

*** According to the International Study Group of Pancreatic Surgery criteria

Table S2. Multivariable analysis for postoperative major morbidity (Clavien-Dindo grade ≥III) and overall survival (since start of treatment) in patients with venous resection

Postoperative major morbidity		**Odds ratio**	**95% CI**		**P-value**
Median annual center volume of venous resections	Below (≤6)	Reference			
	Above (>6)*	0.457	0.208	1.001	0.050
Type of venous resection	Wedge	Reference			
	Segment	2.398	1.248	4.610	0.009
Sex	Male	Reference			
	Female	1.942	1.028	3.666	0.041
Age (years)		0.993	0.959	1.028	0.705
BMI (kg/m^2)		0.956	0.873	1.046	0.324
ASA score	I-II	Reference			
	III-IV	2.574	1.287	5.146	0.007
Preoperative biliary drainage	No	Reference			
	Yes	1.358	0.723	2.552	0.342
Neoadjuvant therapy	No	Reference			
	Yes	1.727	0.689	4.328	0.244
Pancreatic duct diameter (mm)		0.928	0.849	1.014	0.098

Table s2. Continued

Texture pancreatic remnant	Normal/soft	Reference			
	Fibrotic/Hard	0.888	0.460	1.715	0.723
Blood loss during surgery (mL)		1.000	1.000	1.000	0.123

Overall survival		**Hazard ratio**	**95% CI**		**P-value**
Median annual center volume of venous resections	**Below (≤6)**	Reference			
	Above (>6)*	0.600	0.425	0.847	0.004
Type of venous resection	**Wedge**	Reference			
	Segment	1.281	0.949	1.728	0.106
Sex	**Male**	Reference			
	Female	1.105	0.817	1.495	0.517
Age (years)		1.015	0.997	1.033	0.96
BMI (kg/m²)		0.965	0.922	1.009	0.116
ASA score	**I-II**	Reference			
	III-IV	1.666	1.180	2.352	0.004
Neoadjuvant therapy	**No**	Reference			
	Yes	1.001	0.600	1.669	0.997
Resection margin status	**R0**	Reference			
	R1	1.463	1.052	2.035	0.004
Tumor diameter on pathology (mm)		0.990	0.977	1.003	0.136
pN stage	**N0**	Reference			
	N1	0.925	0.636	1.345	0.683
	N2	1.272	0.865	1.870	0.221
pM stage	**M0**	Reference			
	M1	1.007	0.303	3.350	0.991
Tumor differentiation grade	**Good**	Reference			
	Moderate	1.490	0.872	2.546	0.145
	Poor/Undiff.	2.003	1.156	3.468	0.013
Lymphangio invasion	**No**	Reference			
	Yes	0.914	0.666	1.255	0.576
Perineural invasion	**No**	Reference			
	Yes	0.965	0.634	1.469	0.868

Missing values were imputed for pancreatic duct (N=76), texture pancreatic remnant (N=36), blood loss during surgery (N=32), tumor size on pathology (N=3), tumour differentiation grade (N=34), lymphangio invasion (N=71), perineural invasion (N=40)

* Three centers with a median annual center volume of respectively 7, 9, and 13 venous resections

Table S3. Baseline, postoperative and histopathological characteristics of patients with venous resection stratified for median annual center volume of venous resections

		Median annual center volume of venous resections				
		Below (≤9)		Above (>9)*		
		N	%	N	%	P-value
Total		299	85.2	52	14.8	-
Preoperative characteristics						
Sex	**Male**	154	51.5	26	50.0	0.841
	Female	145	48.5	26	50.0	
Age (years), median (IQR)		69 (62-73)		68 (60-74)		0.689
BMI (kg/m²), median (IQR)		23.9 (21.8-26.3)		24.0 (21.5-25.4)		0.454
ECOG	**0-1**	262	88.2	44	84.6	0.466
	2-4	35	11.8	8	15.4	
ASA	**I-II**	231	77.3	42	80.8	0.574
	III-IV	68	22.7	10	19.2	
Preoperative biliary drainage		173	57.9	30	57.7	0.982
Neoadjuvant therapy		28	9.4	16	30.8	<0.001
Preoperative resectability status**	**Resectable**	155	52.7	19	37.3	0.125
	Borderline resectable	113	38.4	26	51.0	
	Locally advanced	26	8.8	6	11.8	
Intraoperative characteristics						
Texture pancreatic remnant	**Normal/Soft**	90	33.6	16	34.0	0.951
	Fibrotic/Hard	178	66.4	31	66.0	
Pancreatic duct diameter in mm, median (IQR)		6 (4-9)		6 (3-8)		0.516
Blood loss during surgery in mL, median (IQR)		900 (500-1500)		525 (400-907)		<0.001
Type of venous resection* **	**Type 1**	160	53.5	37	71.2	0.035
	Type 2	30	10.0	0	0	
	Type 3	86	28.8	11	21.2	
	Type 4	23	7.7	4	7.7	
Postoperative characteristics						
Postoperative PV-SMV thrombosis		32	10.7	2	3.8	0.123
Postoperative mortality		16	5.4	2	3.8	0.650
Postoperative major morbidity		82	27.4	12	23.1	0.513
Overall survival (months), median (95% CI)		13 (11-15)		20 (10-30)		0.099
Adjuvant therapy		189	63.6	47	90.4	<0.001
Histopathological characteristics						
Resection margins status	**R0**	102	34.1	22	42.3	0.254

Table s3. Continued

	R1	197	65.9	30	57.7	
Tumour size on pathology in mm, median (IQR)		34 (26-40)		32 (25-38)		0.436
pN-stage	**No**	77	25.8	16	30.8	0.258
	N1	112	37.5	23	44.2	
	N2	110	36.8	13	25.0	
M-stage	**Mo**	290	97.0	52	100.0	0.205
	M1	9	3.0	0	0.0	
Tumour differentiation grade	**Good**	34	12.8	2	3.9	0.020
	Moderate	139	52.3	37	72.5	
	Poor/Undiff.	93	35.0	12	23.5	
Lymphangio invasion		148	64.3	27	54.0	0.171
Perineural invasion		237	91.2	42	82.4	0.059

* One center with a median annual center volume of 13 venous resections
** According to the Dutch Pancreatic Cancer Group criteria
*** According to the International Study Group of Pancreatic Surgery criteria

Table S4. Multivariable analysis for postoperative major morbidity (Clavien-Dindo grade ≥III) and overall survival (since start of treatment) in patients with venous resection

Postoperative major morbidity		**Odds ratio**	**95% CI**		**P-value**
Median annual center volume of venous resections	**Below (≤9)**	Reference			
	Above (>9)*	0.175	0.021	1.495	0.111
Type of venous resection	**Wedge**	Reference			
	Segment	2.394	1.248	4.590	0.009
Sex	**Male**	Reference			
	Female	1.956	1.038	3.687	0.038
Age (years)		0.989	0.955	1.024	0.544
BMI (kg/m²)		0.968	0.887	1.056	0.459
ASA score	**I-II**	Reference			
	III-IV	2.562	1.286	5.104	0.007
Preoperative biliary drainage	**No**	Reference			
	Yes	1.233	0.658	2.311	0.513
Neoadjuvant therapy	**No**	Reference			
	Yes	1.951	0.759	5.013	0.165
Pancreatic duct diameter (mm)		0.932	0.854	1.016	0.110
Texture pancreatic remnant	**Normal/soft**	Reference			
	Fibrotic/Hard	0.928	0.482	1.788	0.823
Blood loss during surgery (mL)		1.000	1.000	1.001	0.073

Table s4. Continued

Overall survival		Hazard ratio	95% CI		P-value
Median annual center volume of venous resections	**Below (≤9)**	Reference			
	Above (>9)*	0.826	0.536	1.272	0.386
Type of venous resection	**Wedge**	Reference			
	Segment	1.345	0.995	1.817	0.054
Sex	**Male**	Reference			
	Female	1.144	0.846	1.548	0.381
Age (years)		1.011	0.994	1.029	0.193
BMI (kg/m²)		0.976	0.934	1.020	0.281
ASA score	**I-II**	Reference			
	III-IV	1.652	1.173	2.327	0.004
Neoadjuvant therapy	**No**	Reference			
	Yes	0.942	0.557	1.594	0.825
Resection margin status	**R0**	Reference			
	R1	1.506	1.082	2.097	0.015
Tumor diameter on pathology (mm)		0.990	0.977	1.003	0.147
pN stage	**N0**	Reference			
	N1	0.921	0.634	1.339	0.666
	N2	1.226	0.835	1.801	0.289
pM stage	**M0**	Reference			
	M1	0.842	0.256	2.775	0.778
Tumor differentiation grade	**Good**	Reference			
	Moderate	1.526	1.082	2.097	0.125
	Poor/Undiff.	2.084	1.206	3.602	0.009
Lymphangio invasion	**No**	Reference			
	Yes	0.918	0.667	1.263	0.598
Perineural invasion	**No**	Reference			
	Yes	1.077	0.713	1.626	0.725

Missing values were imputed for pancreatic duct (N=76), texture pancreatic remnant (N=36), blood loss during surgery (N=32), tumor size on pathology (N=3), tumour differentiation grade (N=34), lymphangio invasion (N=71), perineural invasion (N=40)

* One center with a median annual center volume of 13 venous resections

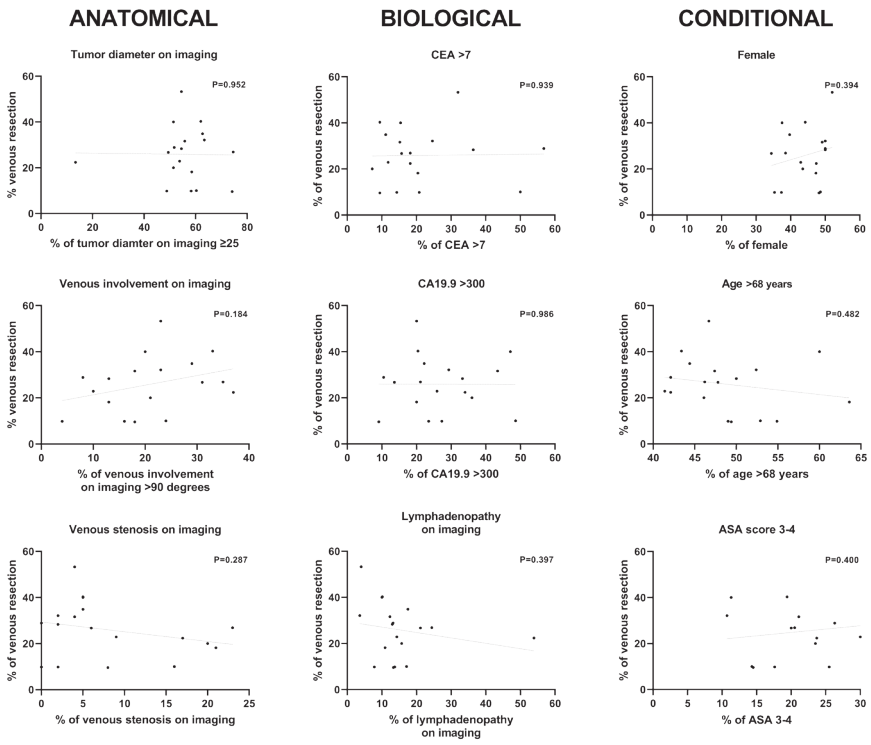

Figure S1. Relationship between rate of venous resections and anatomical, biological and conditional patient characteristics

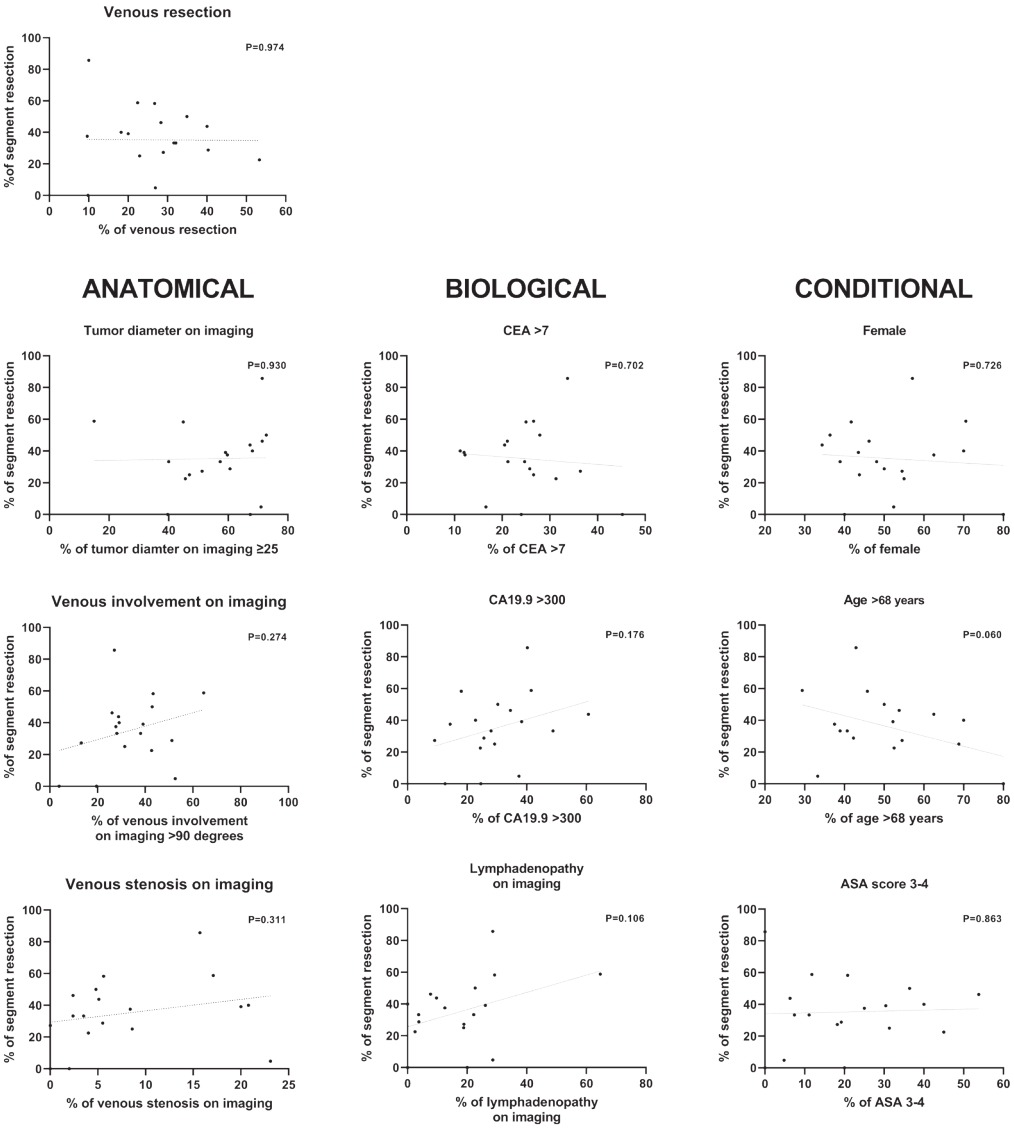

Figure S2. Relationship between venous segment resection and rate of venous resections and anatomical, biological and conditional patient characteristics

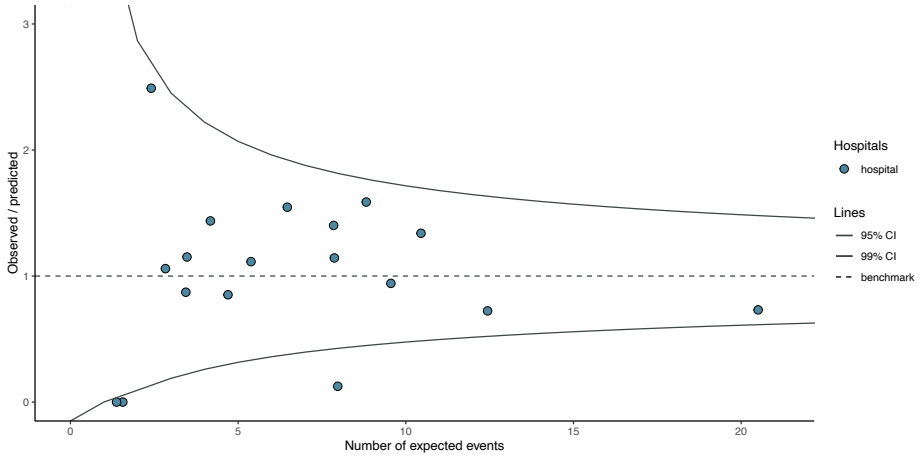

Figure S3. Funnel plot of adjusted center practice variation in the use of venous segment resection during pancreatoduodenectomy for pancreatic cancer (adjusted for neoadjuvant therapy and venous involvement on imaging)

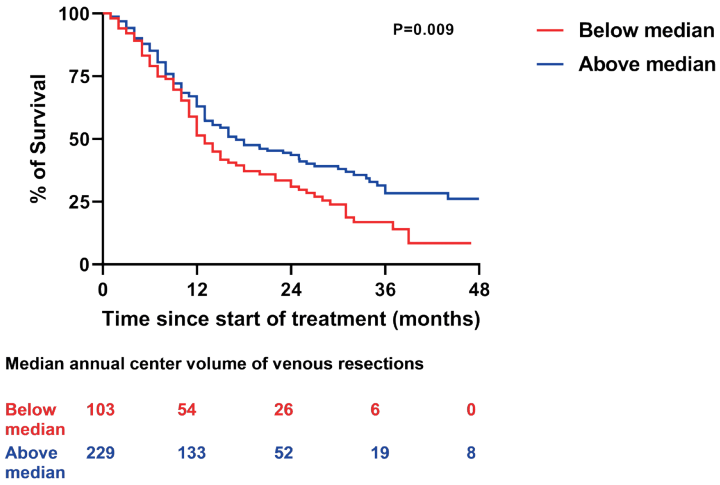

Figure S4. Kaplan–Meier curves of overall survival after start of treatment (day of surgery or start of neoadjuvant therapy) for pancreatic cancer, in patients without postoperative mortality (death within 90 days following surgery), stratified for median annual center volume of venous resections (below: ≤4; above: >4 venous resections)

CHAPTER 8

Resection of the Portal-superior Mesenteric Vein in Pancreatic Cancer: Pathological Assessment and Recurrence Patterns

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ABSTRACT

Objectives: The portal-superior-mesenteric-vein (PV-SMV) margin is the most affected margin in pancreatic cancer. This study investigates the association between venous resection, tumor invasion in the resected PV-SMV, recurrence patterns and overall survival (OS).

Methods: This multicenter cohort study included patients who underwent pancreatoduodenectomy for pancreatic cancer (2010-2017). Additionally, a systematic literature search was performed.

Results: In total, 531 patients were included of which 149 (28%) underwent venous resection of whom 53% had tumor invasion in the resected PV-SMV. Patients with venous resection had a significant higher rate of R1 margins (69% versus 37%) and had more often multiple R1 margins (43% versus 16%). Patient with venous resection had a significant shorter time to locoregional recurrence and a shorter OS (15 vs 19 months). At multivariable analyses, venous resection and tumor invasion in the resected PV-SMV were not predictive for time to recurrence and OS. The literature overview showed that pathological assessment of the resected PV-SMV is not adequately standardized.

Conclusions: Only half of patients with venous resection had pathology confirmed tumor invasion in the resected PV-SMV and both are not independently associated with time to recurrence and OS. The pathological assessment of the resected PV-SMV needs to be standardized.

INTRODUCTION

Invasion of the portal vein (PV) or superior mesenteric vein (SMV) in pancreatic cancer is not considered a contra-indication for resection as published by the International Study Group of Pancreatic Surgery (ISGPS).[1] Two meta-analyses[2,3] concluded that venous resection is the only chance to obtain a R0 margin (possible chance for long-term survival) for patients with invasion of the PV-SMV. Although the meta-analyses reported contradicting mortality and morbidity rates, venous resection is now increasingly performed in patients with pancreatic cancer.[4,5]

One of the main challenges for a pancreatic surgeon when confronted with possible tumor invasion in the PV-SMV is distinguishing tumor from peritumoral inflammation and fibrosis. Tumor invasion in the PV-SMV is reported in 32 to 82% of the patients with venous resection.[6-11] Recent meta-analyses showed that patients with tumor invasion in the resected PV-SMV have a worse overall survival (OS).[11] On the other hand, depth of invasion was not of prognostic value.[12] Both studies highlighted the small and heterogenous cohorts of included studies and the short follow-up. Better understanding of the PV-SMV margin and adequate patient selection for venous resection could improve outcomes, for example by performing extended venous resections in the correctly selected patients in order to achieve a radical resection.

There is important variation in the macro- and microscopic pathological assessment of pancreatoduodenectomy specimen in daily practice.[13] Different grossing techniques are available.[14] Some techniques do describe sampling of the resected PV-SMV, globally[15] or in more detail.[16] Guidelines also differ with respect to the detail of sampling of the resected PV-SMV.[17,18] In an online survey among pathologists who work at institutions which published on venous resection, 78% of pathologists always assess tumor invasion in the resected PV-SMV and only 32% always assess the depth of tumor invasion.[13]

The primary aim of this study was to study the association between venous resection, tumor invasion in the resected PV-SMV, recurrence patterns and OS. Additionally, a systematic literature search was performed to identify large studies (≥500 patients) and to provide an overview of the available evidence regarding this topic.

MATERIALS AND METHODS

Study Design and Patient Selection

This study was a retrospective multicenter cohort study, which included all patients who underwent pancreatoduodenectomy for pancreatic cancer (i.e. pancreatic ductal adenocarcinoma) from January 2010 through December 2017. Approval for this retrospective study was obtained from the Regulatory Boards. All tissue samples were handled in accordance with the medical ethics guidelines described in the Code of Conduct for the Proper Secondary Use of Human Tissue of the Dutch Federation of Biomedical Scientific Societies.[19] The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology criteria.[20]

Data Collection

Prospectively maintained databases were used to identify patients and extract relevant data. Additional data were retrospectively extracted from the medical records. Variables of interest included (mentioned are most relevant)(1) patient-related variables, (2) surgery-related variables: type of venous resection, (3) post-operative variables: adjuvant therapy (4) pathology variables: listing of the venous resection on the pathology request form, tumor diameter, tumor (T), nodes (N), and metastases (M) -staging, tumor differentiation, perineural invasion, lymphovascular-invasion, resection margins, tumor invasion in resected PV-SMV, (5) recurrence and survival variables: recurrence status, date and location, survival status, length of follow-up.

Definitions

Type of venous resection was classified according to the ISGPS guidelines[1] and reported by wedge (Type 1 and 2) or segmental (Type 3 and 4) resection. Tumor (T), nodes (N), and metastases (M) -staging was recoded according to the 8th edition.[17] A R1 margin was defined as tumor cells within 1 mm of the resection margin.[21] The evaluated resection margins were the PV-SMV (i.e. medial, PV-SMV groove), superior mesenteric artery (SMA)(i.e. uncinate), pancreatic, posterior, anterior, bile duct and stomach/duodenum/jejunum (i.e. enteric) resection margins as described by Verbeke and Adsay and recommended by the ISGPS.[1,16,22] Tumor invasion in the resected PV-SMV was scored according to the pathology reports as recommended by the ISGPS.[1] Recurrence was assumed if pathologically confirmed or clinical presentation, biochemical factors (e.g. Cancer Antigen 19-9 serum level) and imaging modalities were highly suggestive for recurrence. Patients visited or were in contact with the outpatients clinic every three months in the first years and thereafter every six months. Date and location (overall recurrence: either locoregional, distant metastasis or both; locoregional: tumor recurrence or lymph nodes in the peripancreatic area; distant metastasis: distant lymph nodes, peritoneum, distant organs) of first recurrence were collected.

Outcomes and Comparisons

The primary outcomes of this study were recurrence patterns and OS. The secondary outcomes were pathology characteristics (mainly tumor invasion in the resected PV-SMV and resection margins). Patients were compared by venous resection (No/Yes) and tumor invasion in the resected PV-SMV (No/Yes).

Literature Overview

A systematic literature search was performed in the MEDLINE, Embase, Web of Science and Cochrane library databases to select relevant studies. Two author (JVG, LvM) screened all titles, abstracts and full-texts independently to determine if studies met the inclusion criteria: reporting ≥500 patients; comparing patients with and without venous resection, with and without tumor invasion in the resected PV-SMV, or by depth of invasion in the resected PV-SMV; written in English; published between January 2009 and October 2019. The reference lists of relevant studies were screened manually to identify additional studies. A predefined standardized data extraction form was used to extract study characteristics (author, journal, country, time period, indications, number of patients, comparisons, percentage of venous resections), pathology characteristics (tumor invasion in the resected PV-SMV, depth of tumor invasion, methods of macro and microscopic pathological assessment of the resected PV-SMV) and recurrence and survival characteristics (overall recurrence, locoregional recurrence and distant metastasis, OS).

Statistical Analysis

For statistical analysis Statistical Package for the Social Sciences for Windows (version 23.0, SPSS, Inc, Armonk, New York) was used. To present continuous variables, median and interquartile range were used. Categorical variables were presented as numbers or percentages. For continuous variables the Mann-Whitney U test was used. For the categorical variables the Chi-square test or Fisher's exact test were used to compare groups. Recurrence and OS were calculated by subtracting the date of event (death/ first recurrence) or last follow-up (censored) from the date of surgery. Recurrence and OS were truncated at 60 months. A Fine-Gray competing risk model was used (R version 3.2.2: cran.r-project.org, R Core Team, Vienna, Austria) for analysis of overall recurrence (competing risk: death), locoregional recurrence (competing risk: distant metastasis and death) and distant metastasis (competing risk: locoregional recurrence and death). Patients with locoregional recurrence and distant metastasis were included in both models. A multivariable Fine-Gray model was used for time to recurrence to adjust for possible confounders. OS was reported with median and 95% confidence interval (C.I.). Kaplan-Meier curves and log-rank tests were used to analyze OS. A multivariable Cox proportional hazard model was used for OS to adjust for possible confounders. $P<0.05$ was considered statistically significant. $P\geq0.05$ was rounded to two decimals.

RESULTS

Baseline Characteristics

In total, 531 patients who underwent pancreatoduodenectomy for pancreatic cancer were included of which 149 (28%) patients underwent a venous resection (Table 1). The yearly rate of venous resections did not increase over the study period (P = 0.31)(Figure S1). Of the patients with a venous resection, 95 (64%) patients underwent wedge resection and 54 (36%) patients underwent segmental resection. Tumor invasion in the resected PV-SMV was observed in 49 out of 92 (53%) of venous resections. Depth of tumor invasion was described in only 21 of these patients: tunica adventitia (n = 1), tunica media (n = 11), tunica intima-lumen (n = 9). The presence of a resected PV-SMV was not mentioned in the pathology request forms of the surgeon in 79 out of 149 (53%) of venous resections. Details regarding tumor invasion in the resected PV-SMV were not mentioned in the pathology report from the pathologist in 57 out of 149 (38%) of venous resections.

Patients with venous resection had a higher Body Mass Index (P = 0.014), had more often neoadjuvant therapy (20% *versus* 8%; P < 0.001) and had a longer duration of surgery (P < 0.001). Other baseline characteristics showed no difference between patients with and without venous resection.

Baseline characteristics showed no difference between patients with and without tumor invasion in the resected PV-SMV, expect for a longer duration of surgery in patients with tumor invasion in the resected PV-SMV (P = 0.027).

Pathology Characteristics

Patients with venous resection had more often R1 resection margins (69% *versus* 37%; P = 0.001), had more often perineural invasion (P = 0.001) and had larger tumors (P < 0.001)(Table 2). The PV-SMV resection margin was the most frequent R1 resection margin, followed by the SMA resection margin. Patients with a venous resection had more often multiple R1 resection margins (43% *versus* 16%; P < 0.001). A minority of patients with and without venous resection had a R1 resection solely at the PV-SMV resection margin (9% and 4%, respectively; P = 0.008). Other pathology characteristics showed no difference between patients with and without venous resection.

Patients with tumor invasion in the resected PV-SMV did not have significantly more often R1 resection margins (78% *versus* 60%; P = 0.08) and did have more often lymphovascular-invasion (P = 0.005). The PV-SMV resection margin was the most frequent R1 resection margin, followed by the SMA resection margin. A minority of patients with and without tumor invasion in the resected PV-SMV had a R1 resection margin solely at the PV-SMV resection margin (14% and 12%, respectively; P = 0.70).

Other pathology characteristics showed no difference between patients with and without venous resection.

Table 1. Patient and surgical characteristics by venous resection and tumor invasion in resected PV-SMV.

		Venous resection					Tumor invasion in resected PV-SMV				
		No		Yes			No		Yes		
		N	%	N	%	P-value	N	%	N	%	P-value
Total		382	71.9	149	28.1	-	43	46.7	49	53.3	-
Sex	**Female**	167	43.7	70	47.0	0.50	21	48.8	22	44.9	0.71
Age (years), median (IQR)		68 (59-73)		66 (60-73)		0.67	65 (59-74)		65 (58-73)		0.77
BMI (kg/m2), median (IQR)		24 (22-25)		23 (22-26)		0.014	24 (22-26)		24 (22-26)		0.80
	Missing	65		26			4		10		
ASA	**III-IV**	67	17.5	30	20.1	0.49	8	18.6	13	26.5	0.37
Preoperative biliary drainage		233	61.0	85	57.0	0.40	21	48.8	28	57.1	0.43
Neoadjuvant therapy		32	8.4	29	19.5	<0.001	10	23.3	7	14.3	0.27
Type of surgery	**PPPD**	253	66.2	104	69.8	0.43	35	81.4	32	65.3	0.08
	Classical Whipple	129	33.8	45	30.2		8	18.6	17	34.7	
Type of venous resection	**Wedge**	-		95	63.8	-	26	60.5	25	51.0	0.36
	Segmental	-		54	36.2		17	39.5	24	49.0	
Additional organ resection		15	3.9	6	4.0	0.96	0		2	4.1	0.18
Duration of surgery (min), median (IQR)		287 (239-349)		333 (281-387)		<0.001	309 (245-363)		345 (298-430)		0.027
	Missing	0		1			0		1		
Blood loss during surgery (ml), median (IQR)		750 (442-1200)		800 (500-1500)		0.06	800 (500-1250)		1000 (500-1510)		0.71
	Missing	30		16			2		7		
Adjuvant therapy		280	73.3	108	72.5	0.85	31	72.1	36	73.5	0.88

PV-SMV: portal vein-superior mesenteric vein; IQR: inter quartile range; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; PPPD: pyloris-preserving pancreatoduodenectomy

Table 2. Pathological characteristics by venous resection and tumor invasion in resected PV-SMV.

		Venous resection					Tumor invasion in resected PV-SMV				
		No		Yes			No		Yes		
		N	%	N	%	P-value	N	%	N	%	P-value
Total		382	71.9	149	28.1	-	43	46.7	49	53.3	-
Tumor invasion in resected PV-SMV	**No**	-		43	46.7	-	-		-		-
	Yes	-		49	53.3		-		-		
	Missing			57							
Tumor size (mm), median (IQR)		29 (22-35)		32 (25-40)		<0.001	30 (25-40)		36 (26-45)		0.10
	Missing	17		4			0		2		
pN-stage	**N0**	96	25.1	43	28.9	0.67	16	37.2	9	18.4	0.12
	N1	149	39.0	54	36.2		12	27.9	19	38.8	
	N2	137	35.9	52	34.9		15	34.9	21	42.9	
pM-stage	**M0**	286	99.7	122	99.2	0.54	43	100	49	100	>0.99
	M1	1	0.3	1	0.8		0		0		
Tumor differentiation	**Good**	39	10.8	14	10.1	0.89	6	14.0	2	4.4	0.30
	Moderate	200	55.6	80	58.0		23	53.5	26	57.8	
	Poor-Undiff.	121	33.6	44	31.9		14	32.6	17	37.8	
	Missing	22		11			0		4		
Lymphovascular-invasion	**No**	206	59.4	70	51.1	0.10	28	66.7	15	35.7	0.005
	Yes	141	40.6	67	48.9		14	33.3	27	64.3	
	Missing	35		12			1		7		
Perineural invasion	**No**	115	31.7	25	17.4	0.001	9	21.4	6	12.5	0.26
	Yes	248	68.3	119	82.6		33	78.6	42	87.5	
	Missing	19		5			1		1		
Resection margin	**R0**	242	63.4	47	31.5	<0.001	17	39.5	11	22.4	0.08
	R1	140	36.6	102	68.5		26	60.5	38	77.6	
PV-SMV resection margin		60	15.7	66	44.3	<0.001	18	41.9	27	55.1	0.21
Solely PV-SMV resection margin		14	3.7	14	9.4	0.008	5	11.6	7	14.3	0.71
SMA resection margin		52	13.6	53	35.6	<0.001	16	37.2	17	34.7	0.81
Pancreatic resection margin		29	7.6	23	15.4	0.006	6	14.0	10	20.4	0.42
Dorsal resection margin		32	8.4	30	20.1	<0.001	4	9.3	11	22.4	0.09
Ventral resection margin		28	7.3	19	12.8	0.048	4	9.3	8	16.3	0.32
Bile duct resection margin		7	1.8	7	4.7	0.06	1	2.3	2	4.1	0.64
Enteric resection margin		4	1.0	2	1.3	0.77	0		2	4.1	0.18
No. of R1 margins	**0**	242	63.4	47	31.5	<0.001	17	39.5	11	22.4	0.21
	1	80	20.9	38	25.5		10	23.3	15	30.6	
	>1	60	15.7	64	43.0		16	37.2	23	46.9	

PV-SMV: portal vein-superior mesenteric vein; IQR: inter quartile range; SMA: superior mesenteric artery

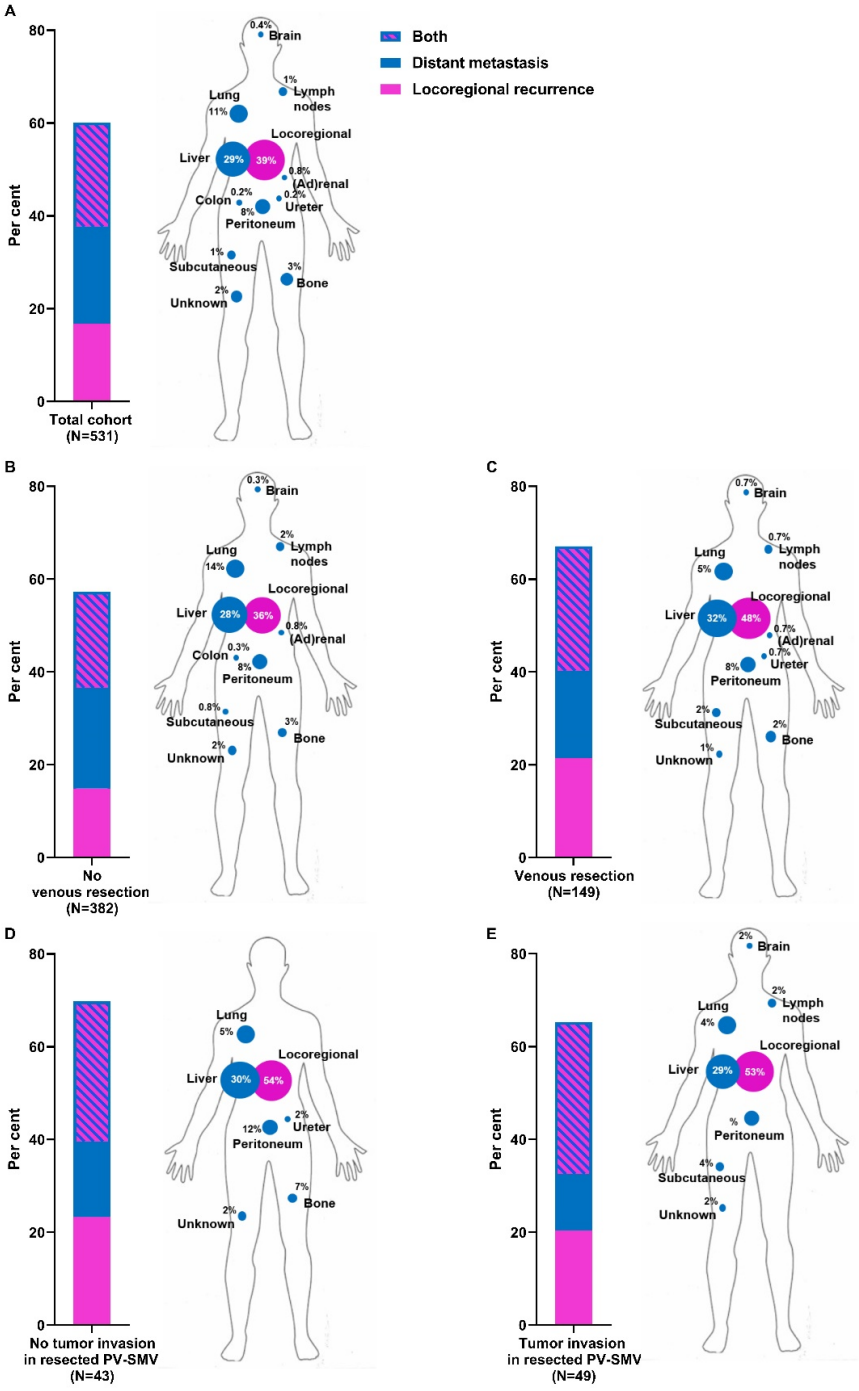

Figure 1A-E. Patterns of recurrence for (A) the total cohort, (B) venous resection, (C) no venous resection, (D) tumor invasion in resected PV-SMV, (E) no tumor invasion in resected PV-SMV.

Recurrence Patterns and Overall Survival

Recurrence Patterns

Patients with and without venous resection showed no difference in pattern of first recurrence: locoregional (22% *versus* 15%), distant metastasis (19% *versus* 22%) or both (27% *versus* 21%)(P = 0.06)(Figure 1B-C). Patient with venous resection had a shorter time to overall recurrence (P = 0.039) and locoregional recurrence (P = 0.013)(Figure 2A-B), though showed no difference in time to distant metastasis (P = 0.46)(Figure 1C). At multivariable analysis, adjusting for radicality and pathological factors, venous resection was not an independent predictor for time to overall recurrence, locoregional recurrence and distant metastasis (Table 3).

Patients with and without tumor invasion in the resected PV-SMV showed no difference in pattern of first recurrence: locoregional (20% *versus* 23%), distant metastasis (12% *versus* 16%) or both (33% *versus* 30%)(P = 0.91)(Figure 1D-E). Patients with and without tumor invasion in the resected PV-SMV showed no difference in time to overall recurrence (P = 0.76), locoregional recurrence (P = 0.97) and distant metastasis (P = 0.84)(Figure 3A-C). At multivariable analysis, adjusting for radicality and pathological factors, tumor invasion in the resected PV-SMV was not an independent predictor for time to overall recurrence, locoregional recurrence and distant metastasis (Table 3).

Overall Survival

Patients with venous resection had a shorter OS (median, 15 [95% C.I., 12-19] *versus* median, 19 [95% C.I., 17-21] months; P = 0.049)(Figure 2D). At multivariable analysis, adjusting for radicality and pathological factors, venous resection was not an independent predictor of OS (Table 3).

Patients with and without tumor invasion in the resected PV-SMV showed no difference in OS (median, 15 [95% C.I., 13-17] *versus* median, 20 [95% C.I., 9-30] months; P = 0.67) (Figure 3D). At multivariable analysis, adjusting for radicality and pathological factors, tumor invasion in the resected PV-SMV was not an independent predictor of OS (Table 3).

Literature Overview

The literature search identified 569 unique studies. After screening of titles and abstracts and full-text review, 16 studies[4-6,10,23-34] met the eligibility criteria (Table 4). The reported rate of venous resections varied from 4 to 46%. Tumor invasion in the resected PV-SMV was observed in 48 to 96% of patients in eight studies. The method of macro and microscopic pathological assessment of the resected PV-SMV was stated in six out of eight studies. Tumor invasion in the resected PV-SMV was scored as no/yes in eight studies, as tunica adventitia/media/intima in two studies, as adventitia/media-intima/lumen in one study, and as superficial (adventitia)/deep (media/intima) in one study.

Table 3. Multivariable analyses for time to overall recurrence, locoregional recurrence, distant metastasis and overall survival by venous resection and tumor invasion in the resected PV-SMV.

		Time to overall recurrence			Time to locoregional recurrence			Time to distant metastasis			Overall survival		
		Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Venous resection*		1.30	0.99-1.70	0.06	1.26	0.91-1.75	0.17	1.25	0.91-1.72	0.17	1.12	0.87-1.44	0.93
R1 resection margins*		1.15	0.91-1.46	0.25	1.77	1.30-2.43	<0.001	0.91	0.68-1.22	0.54	1.30	1.03-1.64	0.030
pN-stage**	**N1**	1.27	0.92-1.75	0.15	0.99	0.68-1.46	0.98	1.21	0.81-1.79	0.36	1.38	1.01-1.90	0.047
	N2	1.72	1.23-2.41	0.002	0.93	0.62-1.41	0.74	1.76	1.17-2.63	0.006	2.12	1.53-2.94	<0.001
Tumor size (mm)		1.00	0.99-1.01	0.97	1.00	0.99-1.01	0.87	1.01	0.99-1.02	0.40	1.01	1.00-1.02	0.06
Perineural invasion*		1.13	0.85-1.51	0.50	1.15	0.79-1.67	0.47	0.96	0.69-1.37	0.81	1.27	0.82-1.97	0.29
Tumor differentiation***	**Moderate**	1.68	1.05-2.71	0.032	1.55	0.89-2.69	0.12	1.64	0.90-2.99	0.11	1.28	0.85-1.93	0.24
	Poor/Undiff.	2.03	1.24-3.33	0.005	1.58	0.89-2.80	0.12	2.05	1.10-3.79	0.023	1.93	1.27-2.93	0.002
Neoadjuvant therapy*		0.93	0.59-1.48	0.76	0.84	0.48-1.46	0.53	0.80	0.46-1.40	0.44	1.27	0.82-1.97	0.29
Adjuvant therapy*		0.97	0.74-1.33	0.98	0.87	0.62-1.22	0.42	1.02	0.73-1.43	0.91	0.52	0.40-0.67	<0.001
Tumor invasion in resected PV-SMV*		1.00	0.60-1.65	0.99	0.95	0.53-1.68	0.85	1.31	0.65-2.63	0.45	1.07	0.64-1.80	0.78
R1 resection margins*		1.87	1.06-3.35	0.032	1.78	0.90-3.46	0.10	1.40	0.73-2.70	0.32	1.59	0.83-3.04	0.16
pN-stage**	**N1**	0.39	0.39-0.90	0.028	0.53	0.24-1.15	0.11	0.38	0.13-1.13	0.08	0.53	0.25-1.15	0.11
	N2	0.87	0.87-1.71	0.69	0.70	0.33-1.49	0.36	1.04	0.49-2.24	0.91	1.45	0.74-2.85	0.28
Tumor differentiation***	**Moderate**	2.64	0.69-10.39	0.17	1.46	0.39-5.48	0.57	4.41	0.51-38.21	0.18	1.66	0.56-4.89	0.36
	Poor/Undiff.	2.10	0.48-9.09	0.32	1.47	0.35-6.25	0.60	4.20	0.46-38.33	0.20	2.08	0.68-6.33	0.20
Adjuvant therapy*		0.48	0.25-0.91	0.023	0.85	0.41-1.76	0.66	0.51	0.23-1.14	0.10	0.37	0.20-0.69	0.002

CI: confidence interval; PV-SMV: portal vein-superior mesenteric vein
*Reference category is 'No'
**Reference category is 'No'
***Reference category is 'Good'

Only one out of eight studies specified whether or not specimens were re-reviewed for study purposes.

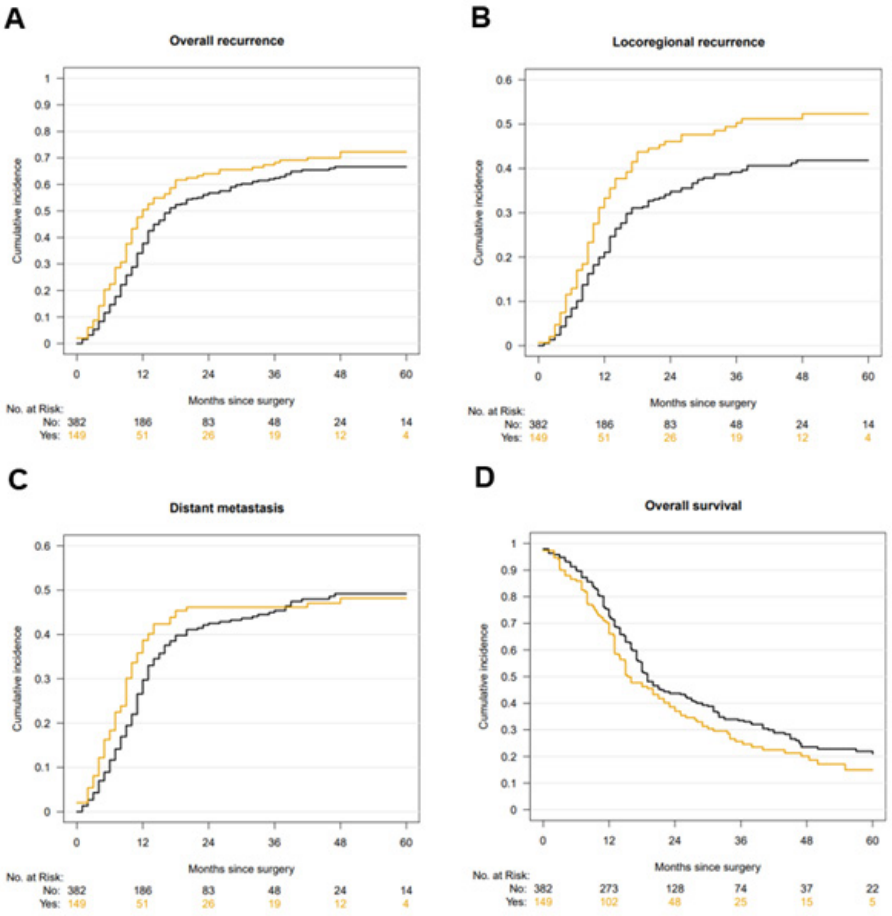

Figure 2A-D. Cumulative incidence curves by venous resection (No/Yes) for (A) overall recurrence (Gray's test: P=0.039), (B) locoregional recurrence (Gray's test: P=0.013), (C) distant metastasis (Gray's test: P=0.46). (D) Kaplan-Meier curve of overall survival by venous resection (No/Yes)(log-rank test: P=0.049).

Data regarding time to recurrence in patients with and without venous resection and with and without tumor invasion in the resected PV-SMV was reported in three studies. Time to recurrence showed no difference between patients with and without venous resection and with and without tumor invasion in the resected PV-SMV in two studies. In one study, patients with tumor invasion in the resected PV-SMV showed a shorter recurrence free survival (median, 11 *versus* median, 16 months; *P* = 0.03).

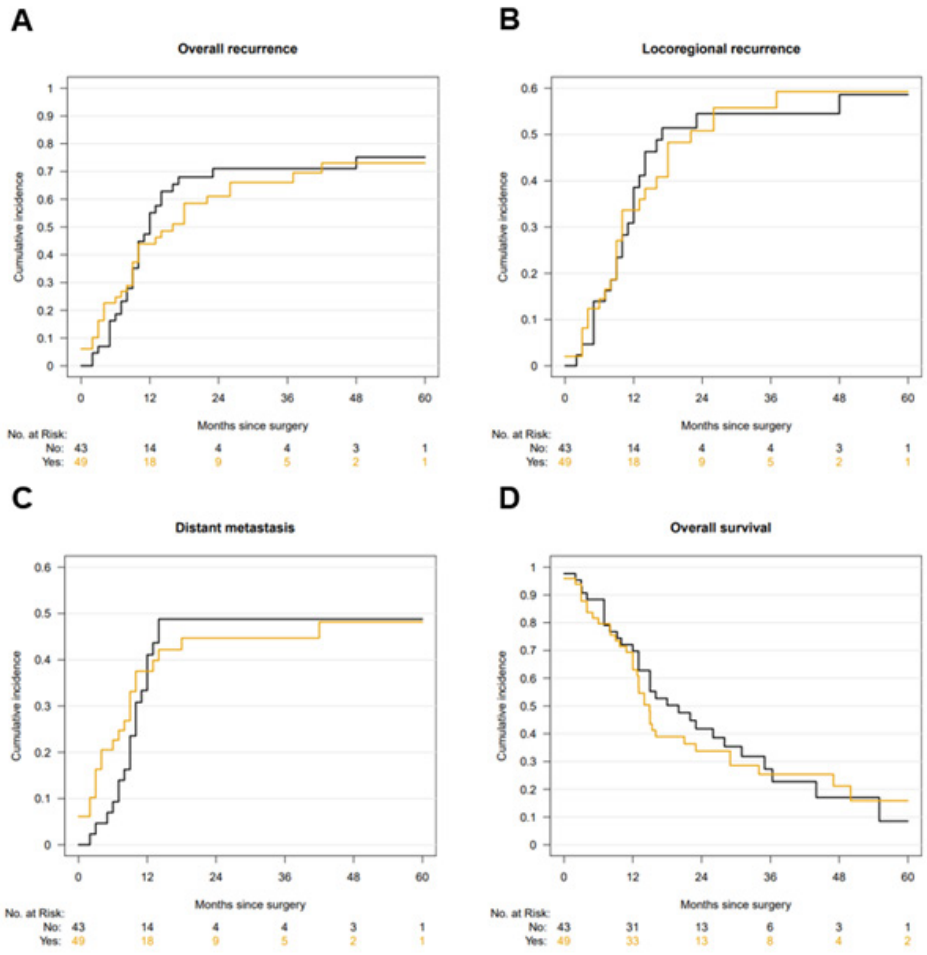

Figure 3A-D. Cumulative incidence curves by tumor invasion in resected PV-SMV (No/Yes) for (A) overall recurrence (Gray's test: P=0.76), (B) locoregional recurrence (Gray's test: P=0.97), (C) distant metastasis (Gray's test: P=0.84). (D) Kaplan-Meier curve of overall survival by tumor invasion in resected PV-SMV (No/Yes)(log-rank test: P=0.67).

Table 4. Overview of large studies (≥500 patients) published in the last decade (2009-2019) on venous resections.

Author	Journal	Country	Time period	Indication	No. patients	Comparison	% of VR	Invasion	Depth of invasion	Methods of macro and microscopic assessment of PV-SMV involvement	Median recurrence free survival in months	Rate of locoregional recurrence	Rate of distant metastasis	Median overall survival in months
Groen	Current study	NL	2010-2017	PDAC	531	VR - / +	28%	53%	Adventitia (N=1) / media (N=11) / intima-lumen (N=9)	Based on pathology reports scored according to the ISGPS. Tumor invasion was scored (No/Yes) and depth of invasion (adventitia/media/ intima-lumen).	Shorter after VR +**** (P=0.039)	36% *versus* 48% (P=0.007)	32% *versus* 46% (P=0.50)	19 *versus* 15 (P=0.049)
						Invasion - / +					Not different* (P=0.76)	54% *versus* 53% (P=0.82)	47% *versus* 45% (P=0.88)	20 *versus* 15 (P=0.67)
Kishi	BJS Open	Japan	2002-2016	PDAC	500	Matched VR - / + without invasion	46%*	55%*	-	Pathologically identified PV invasion to tunica adventitia, media and intima.	16 *versus* 15 (P=0.56)	-	-	32 *versus* 32 (P=0.78)
Kantor	HPB	USA	2006-2013	Malignant neoplasm of the pancreas	9235	VR - / direct repair / graft repair	11%	-	-	-	-	-	-	-
Malleo	Pancreatology	Italy	2000-2013	pT3 PDAC of the head	651	VR - / +	12%	69%	-	Infiltration was defined no/yes and always clearly stated by a specialized staff pathologist.	19 *versus* 18 (P=0.64)	-	-	28 *versus* 26 (P=0.60)
						Invasion - / +		-	-		18 *versus* 18 (P=0.99)	31% *versus* 29% (P=0.85)	53% *versus* 49% (P=0.72)	24 *versus* 27 (P=0.20)
Ravikumar	BJS	UK	1998-2012	pT3 PDAC of the head	1070	Primary closure / end-to-end / graft	22%	48%	Superficial: 27%; Deep: 21%	Portal vein invasion: superficial (tunica adventitia) and deep (invasion to the tunica media or intima).	-	-	-	-
						No invasion / superficial / deep		-	-		-	-	-	-
Kleive	BJS	Norway	2006-2015	All (37% PDAC)	778	VR - / +	16%	-	-	-	-	-	-	-

Table 4. Continued

Roch	J Gastrointest Surg	USA	2000-2014	PDAC	567	VR - / +	16%*	58%	-	Assessed by staff pathologists (not re-reviewed for this study). Infiltration was defined as no/yes. Depth of infiltration was according the deepest tunica (adventitia, media/ intima, and lumen). Tangential margins of the resected vein: not assessed.	13 *versus* 15 (P=0.91)	-	-	20 *versus* 17 (P=0.11)
						Invasion - / +		-	-		11 *versus* 16 (P=0.03)	-	-	20 *versus* 15 (P=0.08)
						Adventitia / media-intima / lumen		-	17% / 65% / 17%		11 *versus* 12 *versus* 5 (P=0.59)	-	-	14 *versus* 16 *versus* 7 (P=0.50)
Elberm	Eur J Surg Oncol	UK	1998-2011	pT3 PDAC of the head	1070	VR - / +	22%	-	-	-	-	-	-	-
Glebova	J Vasc Surg	USA	1970-2014	Cancer	6522	VR - / +	3%	-	-	-	-	-	-	-
						Primary / Vein / Patch / Graft		-	-	-	-	-	-	-
Murakami	BJS	Japan	2001-2012	PDAC of the head	937	VR - / +	46%	60%	-	-	-	-	-	-
						Invasion - / +		-	-	-	-	-	-	-
Hwang	Pancreas	South Korea	2003-2011	PDAC of the head	543	VR - / +	27%	-	-	-	-	-	-	-
Delpero	Ann Surg Oncol	France	2004-2009	PDAC**	1399	VR - / +	29%	56%		-	-	-	-	-
						Lateral / Segmental		-	-	-	-	-	-	-
						Invasion - / +		-	45% Adventitia / 24% media / 32% intima	-	-	-	-	-
Ravikumar	J Am Coll Surg	UK	1998-2011	pT3 PDAC of the head	1070	VR - / +	22%	-	-	Histologic assessment was done at the individual units. Histologic evidence of vascular invasion was not assessed.	-	-	-	-

DISCUSSION

This multicenter study included 531 patients who underwent pancreatoduodenectomy for pancreatic cancer, of which 28% had a venous resection. Tumor invasion in the resected PV-SMV was observed in 53% of venous resections. Patients with a venous resection had more R1 resections and only a few patients had a R1 resection at the PV-SMV resection margin alone. Patients with a venous resection showed shorter time to overall recurrence, locoregional recurrence and shorter OS. Although this effect disappeared when adjusted for radicality and pathological factors. Tumor invasion in the resected PV-SMV was also not associated with recurrence patterns and OS. The literature overview showed that methods of pathological assessment of the resected PV-SMV are often not described in detail. Venous resection and time to recurrence is underreported in current literature.

Only 53% of the resected PV-SMV showed tumor invasion. This is within the range (32-82%) of what is reported in literature[11] and underlines the need for improvement of patient selection. It remains difficult for a surgeon to distinguish tumor from peritumoral inflammation and fibrosis during surgery. Additional tools as intraoperative ultrasound (including contrast enhanced) or Fluorescence-Guided Surgery could be of added value in selecting the right patients who need a venous resection to obtain a radical resection and patients for which a venous resection won't improve outcome.[35-37]

Patients with venous resection had a higher rate of R1 resections (most frequently the PV-SMV and SMA margin) and a higher rate of locoregional recurrence. The area surrounding the PV-SMV and SMA contains a higher density of blood and lymphatic vessels and nerves making invasion of these structures relatively easy.[38,39] A previous study showed that a radical venous resection can rarely be achieved due to the microanatomy at the PV-SMV margin and the broadly invasive growth pattern of pancreatic cancer next to the resected PV-SMV.[40] The fact that only a few patients had a microscopically R1 resection solely at the PV-SMV resection margin indicates that a more extensive resection at this margin is probably often not sufficient to improve radicality. Recent studies suggest that neoadjuvant therapy can improve radicality and OS in (borderline) resectable disease.[41] In locally advanced disease, evidence is growing for neoadjuvant therapy in combination with a TRIANGLE operation[42] (radical tumor removal by sharp dissection along the celiac axis and the superior mesenteric artery with complete dissection of all soft tissue between both arteries and the PV-SMV) and in selected cases also arterial divestment[43] (dissection of periarterial soft tissue around the peripancreatic visceral arteries).

The multivariable analysis showed an independent association between several pathological factors and shorter time to locoregional (mainly R1 resection), shorter time to distant metastasis (mainly pN-stage and tumor differentiation) and worse OS (combination). The causality of these association cannot be confirmed by this study due to its design. The main sites of recurrence were locoregional, liver, peritoneum and lung, which is in line with the literature.[44] A recent retrospective study of the Dutch Pancreatic Cancer Group (DPCG) showed that early detection and initiation of treatment of recurrence may be beneficial for OS.[45] Data regarding venous resection and time to recurrence is only scarcely available in literature. Patients with venous resection might be candidates for close follow-up with a low threshold for biochemical assessment and imaging.[46] However, evidence on standardized follow-up for the detection and treatment of recurrence is limited and currently planned prospective studies within the DPCG will provide useful data.[47]

As in the present study, previous studies have also encountered missing assessments of the resected PV-SMV in pathology reports (38% in this study).[32,48] Unclear or absent marking of the specimen and unclear or absent listing on the pathology request form by the surgeon (53% in this study) makes it difficult for the pathologists to recognize the resected PV-SMV, especially in case of a venous wedge resection.[10] The literature overview showed a lack of standardization regarding the methods of pathological assessment of the resected PV-SMV. This was also found in the previously mentioned survey, as 89% of pathologists expected differences between institutions and pathologists regarding the assessment of venous involvement.[13] Within the DPCG, pathology request forms and pathology reports have now been standardized with regard to assessment of venous involvement. The location of deepest invasion in the resected PV-SMV is assessed and all edges of the resected PV-SMV are assessed for radicality. To improve communication between the surgeon and pathologist, one can consider performing the first macroscopic pathological assessment together. A prospective multicenter study, in which pathological assessment of the venous resection and margins are standardized, is needed in order to investigate the true prognostic value of (depth of) tumor invasion in the resected PV-SMV.

The results of this study should be interpreted in light of several limitations. First, in a retrospective design, the amount and quality of data available from medical records may lead to information and classification bias. This was namely true regarding the availability of data in the pathology reports which could have biased the results (e.g. if data was not missing at random).[49] Second, changing indications from upfront resection to the increasing use of neoadjuvant therapies may have biased the results. Only 11% of patients received neoadjuvant therapy (compared to 28% in the United States[50]) due to the fact that it was mainly administered in a trial setting during the study period.

This limits the generalizability of the results. Third, performing a venous resection is dependent on the judgment and preferences of the surgeon which may hamper direct generalization of results. On the other hand, the proportion of venous resections was comparable to published literature and did not change over the study period. Fourth, time to recurrence in this study is at risk for observer errors due to the unstandardized imaging. This potential bias is largely undertaken by the standardized follow-up at the outpatient clinic in which clinical and biochemical factors were used to determine the need for imaging and the competing risk analysis. Nevertheless, the results from this study must be interpreted with some caution. Strengths of this study include the large cohort of consecutive patients from three high volume Dutch institutions over an eight year period, long median follow up (time to recurrence: 33 months; OS: 42 months), detailed data on recurrence patterns and the literature overview of large studies published in the last decade.

In conclusion, only half of patients with venous resection have tumor invasion in the resected PV-SMV. Patients with venous resection showed more R1 resections of which only a minority have R1 resection at solely the PV-SMV resection margin. Radicality and pathological factors are independently associated with time to recurrence and OS, whereas venous resection and tumor invasion in the resected PV-SMV are not. The pathological assessment of the resected PV-SMV needs to be standardized.

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SUPPLEMENTARY

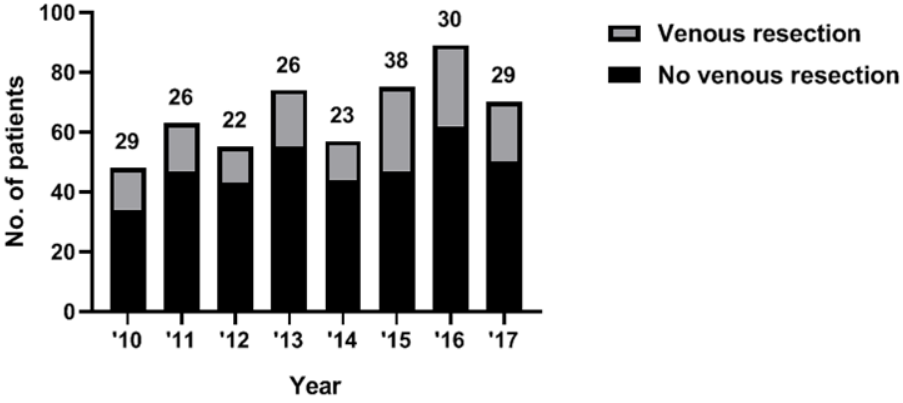

Figure S1. Volume of venous resection over the study period (numbers above bars indicate the percentage of venous resection)($P = 0.31$).

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.

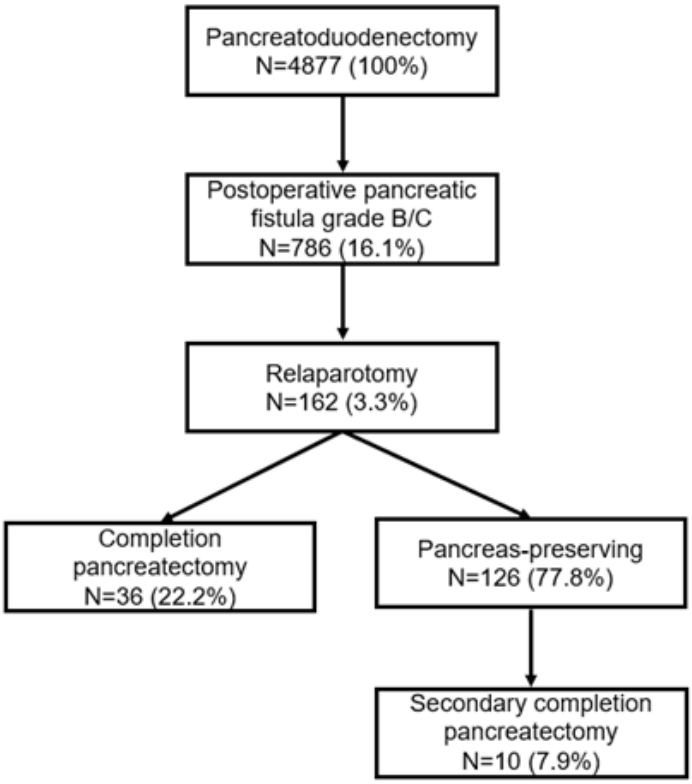

Figure 1. Flowchart of patient selection

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.

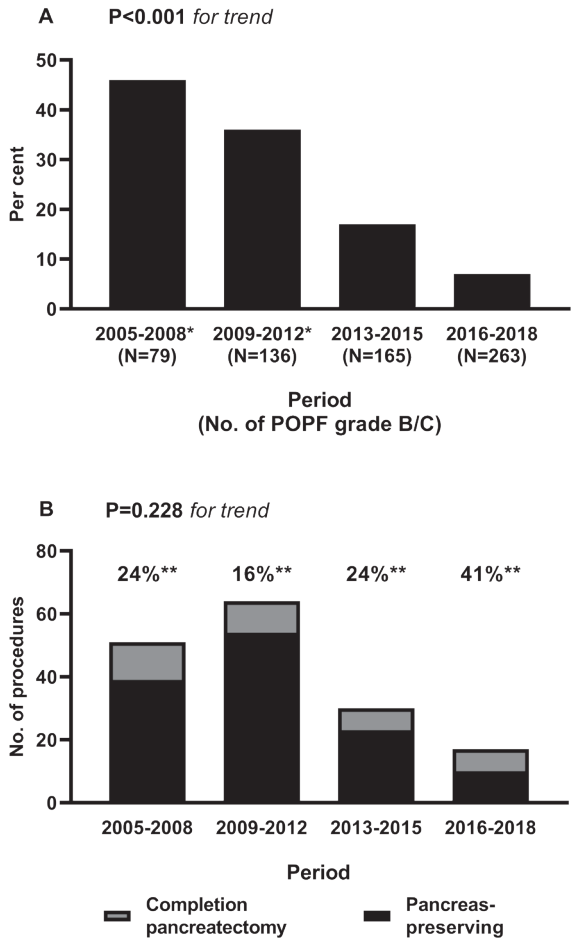

Figure 2. Sensitivity analysis for (A) proportion of patients undergoing relaparotomy for pancreatic fistula (B) and proportion of patients undergoing completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula. *Data from six of nine institutions; **numbers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

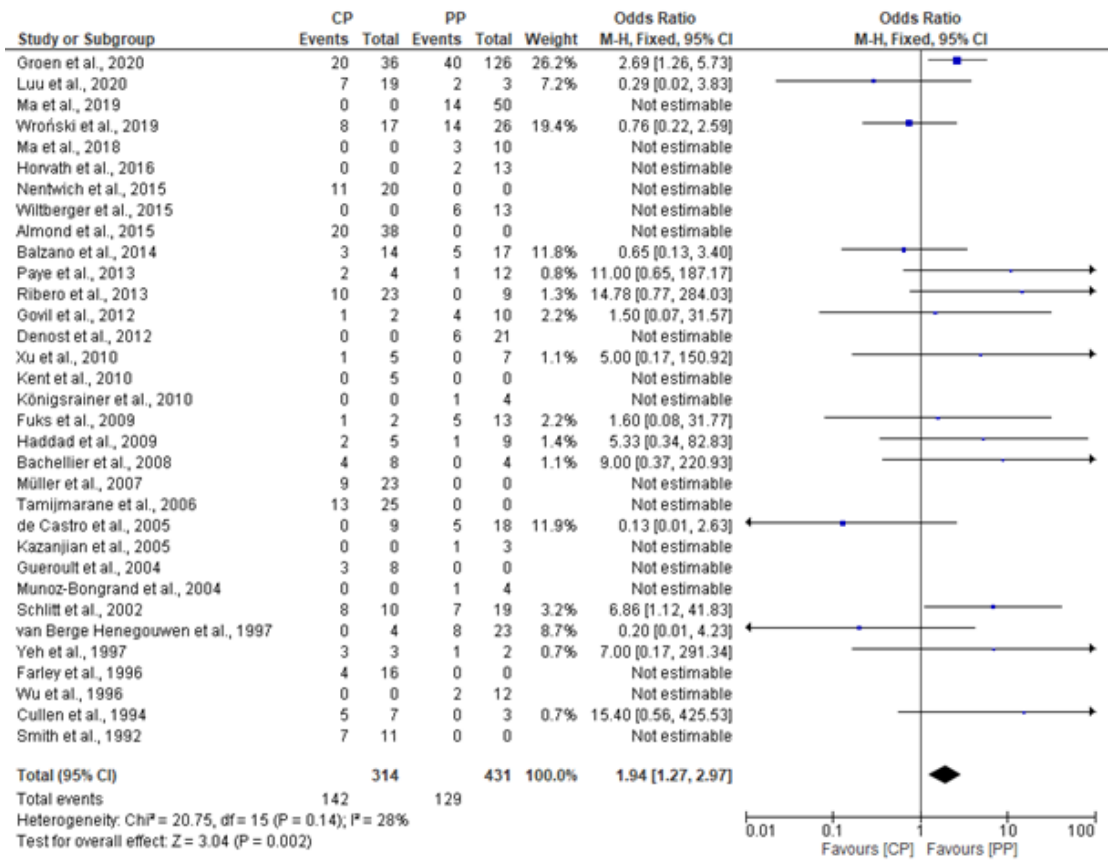

Figure 3. Forest plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) vs pancreas-preserving (PP) (random-effects model)

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)

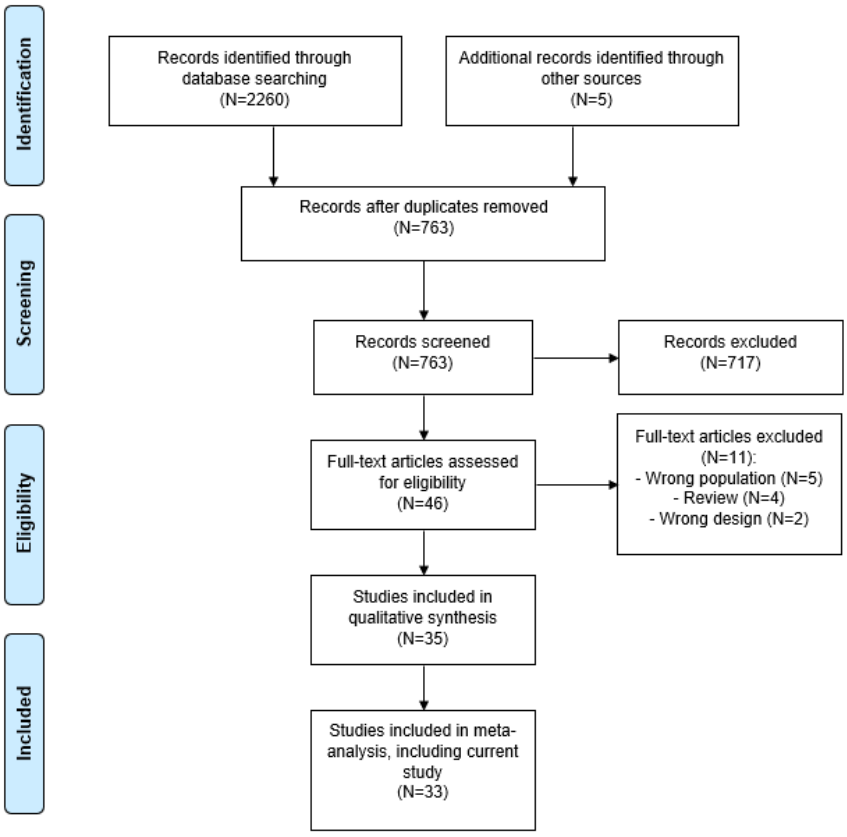

Figure S1. PRISMA flow diagram for the literature search

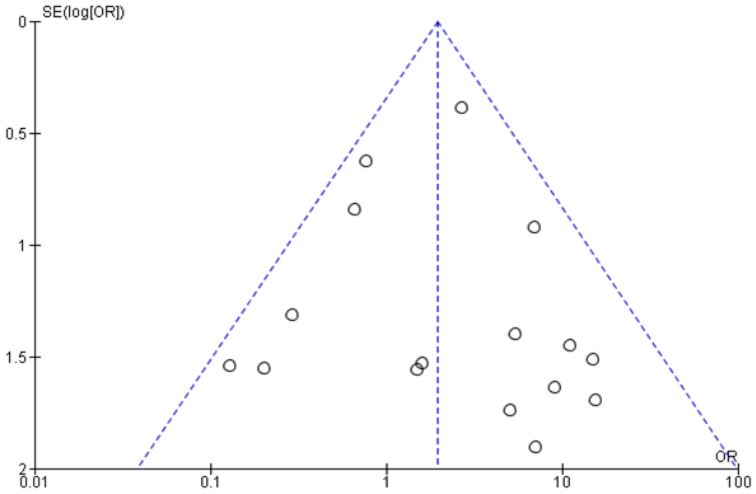

Figure S2. Funnel plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula

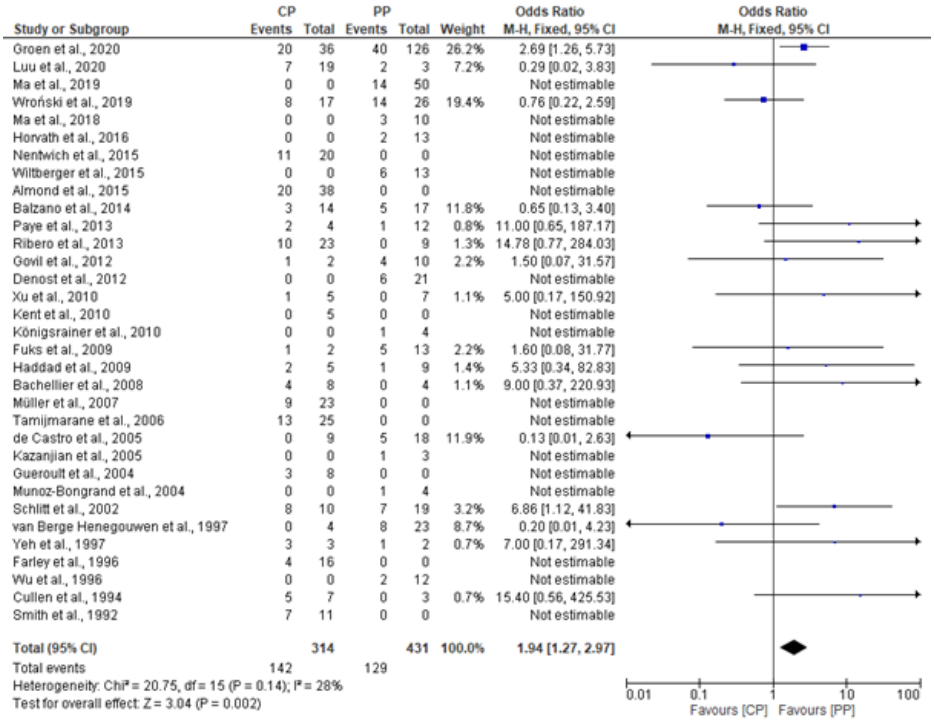

Figure S3. Forest plot of mortality after initial relaparotomy by surgical strategy for pancreatic fistula: completion pancreatectomy (CP) vs pancreas-preserving (PP) (fixed-effects model)

CHAPTER 10

Pancreas-preserving surgical interventions during relaparotomy for pancreatic fistula after pancreatoduodenectomy

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TO THE EDITOR

With great interest we read the study by Garnier et al.[1] regarding their four-step standardized technique during completion pancreatectomy for pancreatic fistula after pancreatoduodenectomy. They conclude that their standardized technique appears to be relatively safe, reproducible, and could be particularly useful for young surgeons. Although we support standardization of this technique, we don't agree with the additional statements that pancreas-preserving surgical interventions are associated with more reoperations and mortality and that simple surgical drainage should not be adopted.

Within the Dutch Pancreatic Cancer Group, we recently compared 36 patients undergoing completion pancreatectomy and 126 patients undergoing a pancreas-preserving intervention during the first relaparotomy for pancreatic fistula after pancreatoduodenectomy.[2] Mortality was higher after completion pancreatectomy (odds ratio after correction for confounders 2.55, 95% confidence interval 1.07-6.08). The proportion of additional reinterventions was not different between groups (64% vs 67%, P=0.76). Additionally, we conducted a meta-analysis on mortality and found a similar association (745 patients, odds ratio 1.99, 95% confidence interval 1.03-3.84).

A subgroup analysis by different pancreas-preserving surgical interventions is shown in Table 1. The groups did not differ at baseline (before first relaparotomy for pancreatic fistula) regarding previous reinterventions, organ failure and APACHE II score. Mortality was 29% following simple surgical drainage vs 37% (range 30-44%) for the other subgroups (P=0.341). Additional reinterventions were performed in 65% following simple surgical drainage vs 70% (range 60-83%) for the other subgroups (P=0.601).

Simple surgical drainage was not associated with more reinterventions or mortality in our cohort compared to other pancreas-preserving surgical interventions. Therefore, we believe that, after failure of percutaneous drainage, simple surgical drainage is a viable option in the management of pancreatic fistula following pancreatoduodenectomy.

Table 1. Subgroup analysis following different surgical interventions during relaparotomy for pancreatic fistula after pancreatoduodenectomy

		Pancreas-preserving surgical interventions during relaparotomy for pancreatic fistula												
		Simple surgical drainage		Other subgroups			Repair of pancreatic anastomosis		DAPR		DAPR with external wirsungostomy		Redo PJ		
		N	%	N	%	P-value[a]	N	%	N	%	N	%	N	%	P-value[b]
Total		80	63.5	46	**36.5**	-	**20**	**15.8**	**12**	**9.5**	**9**	**7.1**	**5**	**4.0**	-
Baseline at time of relaparotomy															
Previous reintervention		33	41.3	24	52.2	0.236	9	45.0	7	58.3	7	77.8	1	20.0	0.166
Organ failure 24h before*	**No**	43	54.4	25	55.6	0.848	14	70.0	7	58.3	3	33.3	1	25.0	0.235
	Single	26	32.9	13	28.9		6	30.0	2	16.7	3	33.3	2	50.0	
	Multiple	10	12.7	7	15.6		0	0	3	25.0	3	33.3	1	25.0	
Highest APACHE II score 24h before*	**Median (IQR)**	11 (8-14)		13 (9-16)		0.116	13 (7-17)		12 (10-16)		13 (12-15)		11 (10-14)		0.606
Postoperative day of first relaparotomy	**Median (IQR)**	9 (7-15)		10 (6-14)		0.871	10 (7-14)		13 (7-15)		9 (5-14)		4 (2-10)		0.668
Main outcomes after relaparotomy															
Mortality		23	28.8	17	37.0	0.341	6	30.0	5	41.7	4	44.4	2	40.0	0.785
Organ failure 24h after*	**No**	22	27.8	12	26.7	0. 752	7	35.0	3	25.0	1	11.1	1	20.0	0.894
	Single	18	22.8	8	17.8		4	20.0	2	16.7	1	11.1	1	25.0	
	Multiple	39	49.4	25	55.6		8	40.0	7	58.3	7	77.8	2	50.0	
Highest APACHE II score 24h after*	**Median (IQR)**	13 (11-17)		17 (13-21)		0.001	17 (11-21)		18 (16-23)		16 (14-21)		15 (15-17)		0.013
Additional reintervention		52	65.0	32	69.6	0.601	16	80.0	10	83.3	7	77.8	3	60.0	0.627
Secondary completion pancreatectomy		3	3.8	7	15.2	0.022	4	20.0	2	16.7	1	1.11	0		0.103

Abbreviations: DAPR: disconnection of pancreatic anastomosis with preservation of remnant; PJ: pancreatojejunostomy; APACHE: Acute Physiology And Chronic Health Evaluation; IQR: interquartile range

*Missing data: organ failure 24h before (N=2), highest APACHE II score 24h before (N=14), organ failure 24h after (N=2), highest APACHE II score 24h after (N=15)

[a] Comparison between simple surgical drainage and other subgroups

[b] Comparison between all pancreas-preserving interventions

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CHAPTER 11

Clinical implications of bile cultures obtained during pancreatoduodenectomy: a cohort study and meta-analysis

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ABSTRACT

Background: The association between intraoperative bile cultures and infectious complications after pancreatoduodenectomy remains unclear. This cohort study and meta-analysis aimed to determine the predictive role of intraoperative bile cultures in abdominal infectious complications after pancreatoduodenectomy.

Methods: The cohort study included 114 patients undergoing pancreatoduodenectomy. Regression analyses were used to estimate the odds to develop an organ space infection (OSI) or isolated OSI (OSIs without a simultaneous complication potentially contaminating the intraabdominal space) after a positive bile culture. A systematic review and meta-analysis was performed on abdominal infectious complications (Mantel-Haenszel fixed-effect model).

Results: The positive bile culture rate was 61%, predominantly in patients after preoperative biliary drainage (98% vs 26%, $p<0.001$). OSIs occurred in 35 patients (31%) and isolated OSIs in nine patients (8%) and were not associated with positive bile cultures (OSIs: odds ratio=0.6, 95% CI=0.25-1.23, isolated OSIs: odds ratio=0.77, 95% CI=0.20-3.04). In the meta-analysis, 15 studies reporting on 2 047 patients showed no association between positive bile cultures and abdominal infectious complications (pooled odds ratio=1.3, 95% CI=0.98-1.65).

Discussion: Given the rare occurrence of isolated OSIs and similar odds for patients with positive and negative bile cultures to develop abdominal infectious complications, routine performance of bile cultures should be reconsidered

INTRODUCTION

Pancreatoduodenectomy remains a complex and technically demanding procedure with high rates of morbidity (25-52%) and mortality (1-3%).[1-4] Infectious complications, such as surgical site infections (SSIs) and organ space infections (OSIs), are reported as the most common complications following pancreatoduodenectomy besides pancreatic fistula and delayed gastric emptying.[5, 6] Previous studies showed an association between preoperative biliary drainage, contamination of intraoperative bile cultures (IOBCs) and the occurrence of postoperative infectious complications, particularly SSIs.[1, 7-10] Although biliary drainage is not routinely recommended, the number of patients requiring this preoperative procedure is expected to rise due to the increasing use of neoadjuvant chemotherapy in pancreatic cancer.[11, 12]

Patients with a biliary stent appear to have different IOBC contamination patterns.[3, 4, 8] Also, neoadjuvant treatment is associated with an alteration of the biliary microbiome.[13] A study in three centers (two USA, one Italian) showed interinstitutional variability in IOBCs and antibiotic resistance patterns, recommending institution-specific reviews to amend protocols for antibiotic prophylaxis.[14] A Dutch study showed appropriate antimicrobial coverage of IOBC microorganisms in 56% of the patients with biliary drainage and in 88% of the patients without biliary drainage.[15] These findings question whether coverage of biliary microorganisms by current antibiotic prophylaxis is sufficient.

The current perioperative antibiotic prophylaxis, generally cefazolin and metronidazole, is used by most centers to prevent SSIs.[16] However, different antibiotic regimens are used as postoperative prophylaxis to prevent OSIs. The clinical impact of bile culture based prophylactic antibiotic treatment, especially in OSIs, is questionable. Several studies concluded that the use of IOBCs does not offer additional information for postoperative infectious complications.[17, 18] Besides, poor concordance between bile cultures and cultures from infectious sites was observed, implicating that IOBC-targeted treatment could lead to the inappropriate use of antibiotics.[19]

Hence, no consensus is achieved about the predictive role of bile cultures in abdominal infectious complications after pancreatoduodenectomy. The primary objective of this study was to investigate the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy. Secondary, the predictive role of IOBCs was evaluated by determining microorganism concordance in bile and OSI cultures. Additionally, a systematic review and meta-analysis was performed to place findings of the current study in perspective of the existing literature.

METHODS

Study design & patient selection

This study was a prospective single-center cohort study, reported according to the STROBE criteria.[20] All patients undergoing pancreatoduodenectomy at the Leiden University Medical Center (LUMC), a tertiary referral center, from June 2016 through October 2019 with an intraoperative bile culture were included. The need for informed consent was waived by the Medical Ethics Committee of the LUMC.

Data collection

Data was collected from the mandatory Dutch Pancreatic Cancer Audit.[21] Additional clinical outcomes were extracted from patient's medical records based on the clinical evaluation of physicians. Variables of interest included patient characteristics (age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score), surgical related information, postoperative complications (e.g. OSIs, SSIs and pancreatic fistula), preoperative biliary drainage and IOBC outcomes and peri- and postoperative antibiotic prophylaxis. Follow-up was up to 30 days after surgery. Two authors (JVG & DHMD) independently performed data collection for OSIs and SSIs; a third independent investigator (JSDM) was consulted in the event of disagreement.

Definitions

Pancreatoduodenectomy included classical Whipple procedures, pylorus-preserving and pylorus-resecting pancreatoduodenectomies. Positive IOBCs or postoperative cultures were defined as the presence of any cultivated microorganism. OSIs and SSIs, classified as superficial incisional SSI or deep incisional SSI, were defined by the Center of Disease Control definition and diagnosed up until 30 days after surgery (supplemental material 1).[22] Due to this comprehensive description, other complications with a non-infectious origin, for instance pancreatic fistula, interfere with the OSI definition by contamination of the intraabdominal space.[10] To decrease the interference of confounding complications, we formulated the concept of isolated OSI to identify 'isolated' abdominal complications such as abdominal abscesses. An isolated OSI was defined as a postoperative OSI occurring within 30 days after surgery without simultaneous occurrence of complications potentially contaminating the intraabdominal space, such as pancreatic fistula, biliary leakage, intestinal anastomotic leakage or gastro-intestinal perforation (defined as gastric or intestinal wall discontinuity confirmed by surgery). Pancreatic fistula and bile leakage were defined and classified according to the International Study Group of Pancreatic Surgery definition.[23, 24]

Microbiological procedures

IOBCs were perioperatively obtained directly after transection of the common bile duct. Assessment of the IOBCs was performed at the Medical Microbiology laboratory according to laboratory's standard operating procedure. In short, selective and nonselective media and broth enrichment were used for culture and incubated both aerobically and non-aerobically at 35˚C. Bacteria were identified when less than two species were growing on the plates, when virulent bacteria were suspected (e.g. *Pseudomonas aeruginosa, Staphylococcus aureus, β-hemolytic Streptococci and Clostridium perfringens*) and if any colony grew on selective culture plates for resistant pathogens. Bacteria were categorized as mixed, fecal or skin flora in case of >2 species not suspected for clinical relevance and IOBCs as positive or negative. OSIs were often treated by placement of abdominal drains by a radiological intervention. Cultures of OSIs were obtained from these abdominal drains within 24h after placement to distinguish infection from colonization or contamination.[25, 26] OSI cultures were analyzed to identify clinically relevant microorganisms and determine resistance patterns.

Antibiotic prophylactic treatment

Standard antibiotic prophylaxis consisted of perioperatively intravenous (IV) cefazolin and 500 mg IV metronidazole, as proposed by Dutch antibiotics guidelines.[27] Due to a change in national protocol, patients undergoing surgery after October 2018 received 2 g instead of 1 g cefazolin every four hours. Doses of 3 g cefazolin were indicated for patients with a BMI >40. Standard postoperative prophylaxis contained five days of 750 mg IV cefuroxime and 500 mg IV metronidazole three times daily according to the local hospital protocol which conformed to the Dutch antibiotic guidelines.[27]

Outcomes and comparison

The main outcomes were the rate of OSIs and isolated OSIs stratified for IOBC status. Secondary outcomes were SSIs, timing of the infectious complications, amount (none, single or multiple) and concordance of microorganisms in IOBCs and postoperative cultures. A Dutch study showed that abdominal drain placement as treatment for pancreatic fistula is generally performed at median postoperative day 9 (interquartile range 7-11 days).[28] To diminish the interference of pancreatic fistula and other complications contaminating the intraabdominal space, analyses of the concordance between IOBCs and cultures from isolated OSIs and OSIs were limited to this time frame. Comparisons were made for patients with positive versus negative IOBCs with stratification for biliary drainage in subgroup analyses.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0. Continuous variables were presented as median with interquartile range, whereas categorical variables were expressed as absolute numbers and percentages. For comparison of continuous variables, the Mann-Whitney U test was performed. Categorical data were analyzed using the chi-squared test or the Fisher's exact test in case of small groups of <20 patients. Binary logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for OSIs, isolated OSIs within seven postoperative days and SSIs. A p-value <0.05 was considered statistically significant.

Systematic review of literature and meta-analysis

A systematic literature search was performed according to the PRISMA statement.[29] PubMed, Embase, Web of Science, COCHRANE Library, Academic Search Premier and PubMed Central were searched for full-text, English-written articles investigating the role of IOBCs in postoperative infectious complications. Titles, abstracts and full-text articles were screened by two independent authors (JVG & DHMD) for eligibility. Articles were selected if a comparison was made for patients with positive and negative IOBCs and study outcomes included postoperative infectious complications. Literature reviews, case reports and case series were excluded. Data extraction was performed using a standardized form with study characteristics, methods of IOBC assessment, number of patients with biliary drainage, IOBCs characteristics and postoperative infectious complications. The risk of bias was determined using the ROBINS-I tool for cohort studies.[30] Quantitative analysis on the primary outcomes (abdominal infectious complications such as OSIs, intraabdominal infections or abscesses and wound infections) was performed using Review Manager (RevMan version 5.3). To assess heterogeneity between studies, the I^2 statistic was used. An I^2 value of >50% was considered to represent substantial heterogeneity. The Mantel-Haenszel fixed-effect model was used to calculate pooled effects, represented as OR and 95% CI.

RESULTS

Patient characteristics

Of the 133 consecutive patients undergoing pancreatoduodenectomy from June 2016 until October 2019, 114 patients with an obtained IOBC were included (Table 1). Baseline characteristics (notably age, ASA score and BMI) of the nineteen patients without obtained bile cultures were comparable to the 114 included patients (data not shown). In nine patients, bile cultures were not performed because of robotic surgery. Preoperative biliary drainage was performed in 56 of the 114 patients (49%). A number of 103 patients received postoperative antibiotic prophylaxis by protocol, which was comparable in

patients with and without biliary drainage (86% versus 95%). Reasons for adjustments in postoperative prophylaxis were postoperative fever or sepsis (n=7), preoperative infections (n=2), adjustments based on postoperative cultures (n=1) or allergies (n=1). Bile cultures were positive in 70 patients: 55 patients with and 15 patients without a biliary stent (98% versus 26%, $p<0.001$). Multiple microorganisms were cultured in 55 IOBCs; in 47 patients with and eight patients without biliary drainage (84% versus 14%, $p<0.001$). Of the 15 patients without biliary drainage and a positive IOBC, 12 patients underwent a preoperative endoscopic retrograde cholangiopancreatography (ERCP) or had a periampullary malignancy versus two of the 43 patients with a negative IOBC without biliary drainage (80% versus 0.05%, p<0.001).

Table 1. Baseline characteristics

				Preoperative biliary drainage				
		Total		No		Yes		
		N	%	N	%	N	%	P
Total		114	100	58	50.9	56	49.1	
Sex	**Male**	68	59.6	32	55.2	36	64.3	0.321
	Female	46	40.4	26	44.8	20	35.7	
Age (years), median (IQR)		68 (59-74)		68 (59-73)		68 (59-74)		0.766
BMI (kg/m²), median (IQR)		25.3 (23.1-28.4)		25.7 (23.0-28.1)		25.1 (23.3-28.6)		0.786
ASA groups	**I-II**	88	77.2	48	82.8	40	71.4	0.149
	III-IV	26	22.8	10	17.2	16	28.6	
Type of surgery	**Classical**	47	41.2	21	36.2	26	46.3	
	PPPD	65	57.0	35	60.3	30	53.6	0.237
	PRPD	2	1.8	2	3.4	0	0.0	
Blood loss (mL), median (IQR)		1000 (750-1400)		1000 (530-1250)		1000 (800-1400)		0.147
Duration of surgery (min), median (IQR)		261 (240-309)		253 (226-291)		273 (245-324)		0.005
Additional resection		8	7.0	6	10.3	2	3.6	0.157
Venous resection		15	13.2	6	10.3	9	16.1	0.366
Arterial resection		1	0.9	0	0.0	1	1.8	0.307
Postoperative antibiotics per protocol*		103	90.4	55	94.8	48	85.7	0.099
IOBCs	**Positive**	70	61.4	15	25.9	55	98.2	<0.001
	Negative	44	38.6	43	74.1	1	1.8	
Microorganisms in IOBC	**Multiple**	55	48.2	8	13.8	47	83.9	
	Single	15	13.2	7	12.1	8	14.3	<0.001
	None	44	38.6	43	74.1	1	1.8	

*Cefuroxime and metronidazole for five days. IQR: Interquartile range. BMI: Body Mass Index. ASA: American Society of Anesthesiologists. Classical: Whipple pancreatoduodenectomy. PPPD: pylorus preserving pancreatoduodenectomy. PRPD: pylorus resecting pancreatoduodenectomy. IOBC: intraoperative bile culture

Primary outcome

OSIs occurred in 35 patients (31%); 18 patients (26%) with positive and 17 (39%) with negative IOBCs (OR=0.6, 95% CI=0.25-1.23. Table 2). After stratification for biliary drainage, OSI rates remained comparable for positive and negative IOBCs in patients without a biliary stent (35% and 37%). Isolated OSIs occurred in nine patients (8%): five patients with positive and four with negative IOBCs (OR=0.77, 95% CI=0.20-3.04). OSIs were not isolated in 26 patients, mainly because of simultaneous occurrence of pancreatic fistula in 21 patients (81%).

Table 2. Infectious complications

				Intraoperative bile culture				
		Total (n=114)		Negative (n=44)		Positive (n=70)		
		N	%	N	%	N	%	P
OSI		35	31	17	39	18	26	0.145
Timing	**1-7 Days**	15	13	5	11	10	14	0.076
	8-14 Days	9	8	7	16	2	3	
	>14 Days	11	10	5	11	6	9	
Isolated OSIs*		9	8	4	9	5	7	0.707
Timing	**1-7 Days**	4	4	1	2	3	4	0.316
	8-14 Days	2	2	2	5	0	0	
	>14 Days	3	3	1	2	2	3	
OSIs with simultaneous occurrence of confounding complications		26	23	*13*	*30*	*13*	*19*	0.774
	Pancreatic fistula	21	18	11	25	10	14	0.581
	Biliary leakage	3	3	2	5	1	1	0.512
	Enteric leakage or perforation	2	2	0	0	2	3	0.157
SSI		22	19	8	18	14	20	0.811
Location	**Superficial**	19	17	7	16	12	17	0.965
	Deep	3	3	1	2	2	3	
Timing	**1-7 Days**	8	7	3	7	5	7	0.947
	8-14 Days	7	6	2	5	5	7	
	>14 Days	7	6	3	7	4	6	

OSI: Organ Space Infection. SSI: Surgical Site Infection.
* OSIs in absence of confounding postoperative complications

Secondary outcomes

SSIs occurred in 22 patients (19%), of which 19 patients had superficial and three patients had deep incisional SSIs (Table 2). SSIs developed in 14 patients with positive and eight patients with negative IOBCs (OR=1.1, 95% CI=0.43-2.95). SSI rates remained comparable in patients with positive and negative IOBCs after stratification for biliary stenting (data not presented).

Isolated OSIs were not more observed in the first postoperative week compared to the second postoperative week or later after pancreatoduodenectomy. Isolated OSIs within seven days after surgery developed in three patients (4%) with positive and one (1%) with a negative IOBC (OR=1.9, 95% CI=0.19-19.10).

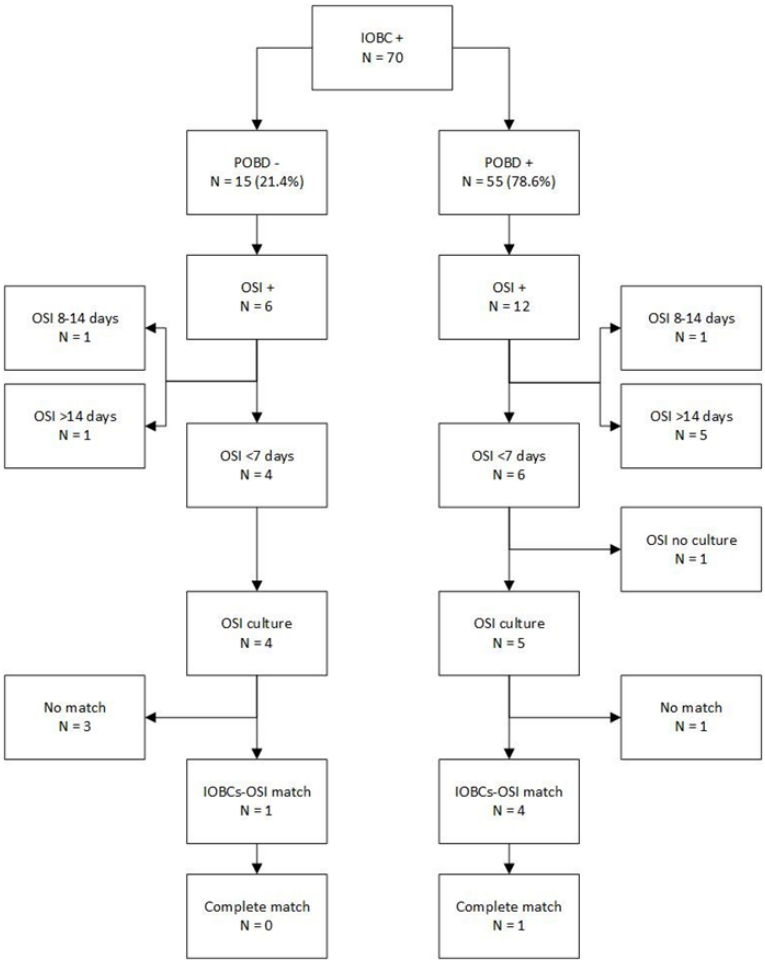

Figure 1. Culture concordance between bile and OSI cultures in patients with OSIs within seven days after pancreatoduodenectomy.

Multi-drug resistant organisms (MDRO) were cultivated from the IOBCs of three patients (3%). Detailed analysis of the microorganisms cultured from OSIs was performed in patients who developed an OSI or isolated OSI within seven days after surgery (n=15). Nine patients had both a positive IOBC and an obtained OSI culture (Figure 1). Partial microorganism concordance between bile and OSI cultures was observed in five of the nine patients. Complete concordance was seen in one out of nine patients.

Systematic review of literature and meta-analysis

The literature search identified 526 studies. After screening titles, abstracts and full-texts, 17 studies were included (Figure 2).[1, 6, 7, 9, 14, 19, 31-41] The selected studies included one prospective and 16 retrospective cohort studies evaluating IOBCs obtained during pancreatoduodenectomy (supplemental material 3). Three studies reported detailed information about the microbiological assessment of IOBCs[36, 38, 39], while the remaining 14 studies either did not report these methods or reported them as standard laboratory's procedures. Various definitions were used for wound infections, OSIs, abdominal infections and abscesses. The studies did not report on isolated abdominal infections or time-depending infectious complications after pancreatoduodenectomy. Most of the studies were qualified as having a moderate risk of bias, but four studies were assessed to have a serious risk of bias (supplemental material 4). Reasons for elevated risks of bias were mostly the absence of clear definitions for infectious outcomes or different antimicrobial regimes in the groups with positive and negative bile cultures.

The reported percentage of positive IOBCs varied from 40-90%.[1, 6, 7, 9, 19, 31-41] Positive IOBCs were more often observed in patients with biliary drainage (median 88%, range 47-100% versus median 29%, range 5-57%). The quantitative analysis included 15 of the selected studies and the current study (Figure 3). Fifteen studies, including the current study, reported on OSIs, abdominal infections or abdominal abscesses in 2 047 patients and showed comparable rates of abdominal infectious complications in patients with positive and negative IOBCs (OR=1.3, 95% CI=0.98-1.65, I^2=38%, figure 3A). Fourteen studies, including the current study, reported on surgical site infections or wound infections in 2 064 patients and observed an association between positive bile cultures and wound infections (OR=3.5, 95% CI=2.65-4.61. I^2=0%. Figure 3B). The funnel plots showed a nearly symmetrical scatter around the mean for all outcomes (supplemental material 5). Sensitivity analyses with a random-effects model showed similar results for both OSIs and SSIs (supplemental material 6).

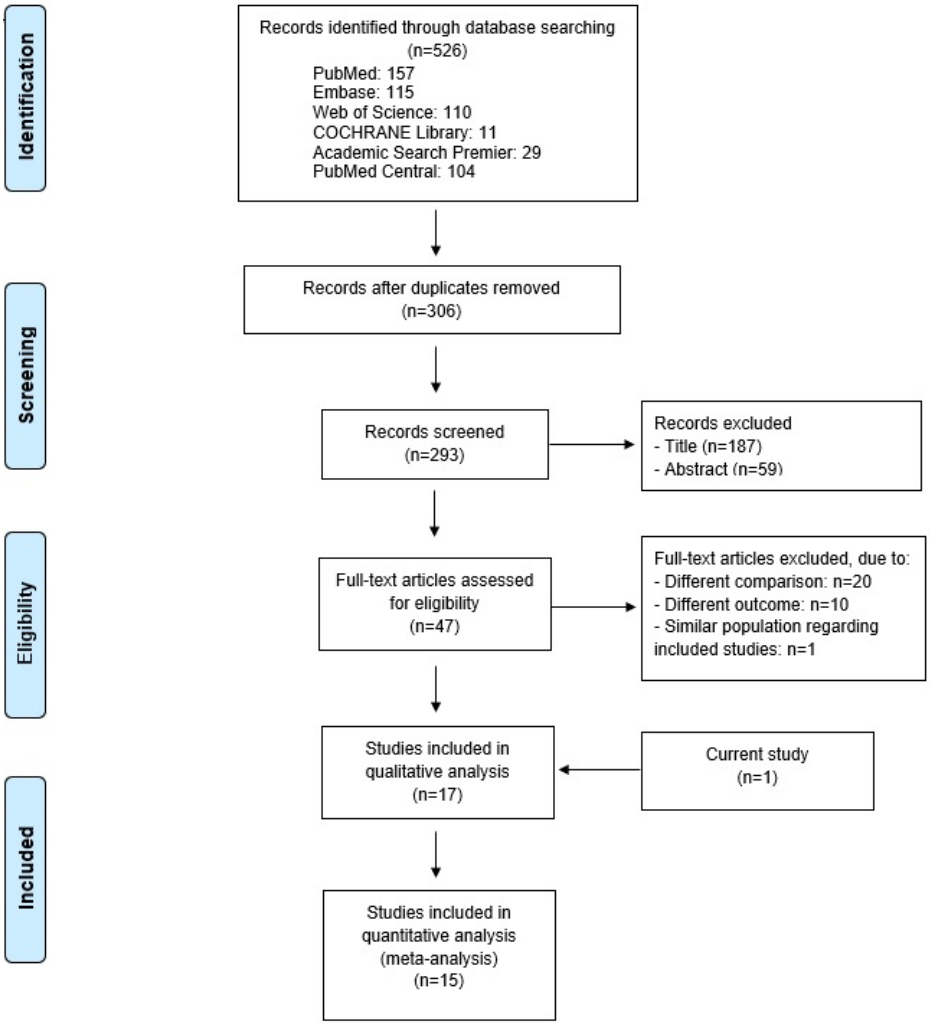

Figure 2. Study selection for the systematic review and meta-analysis

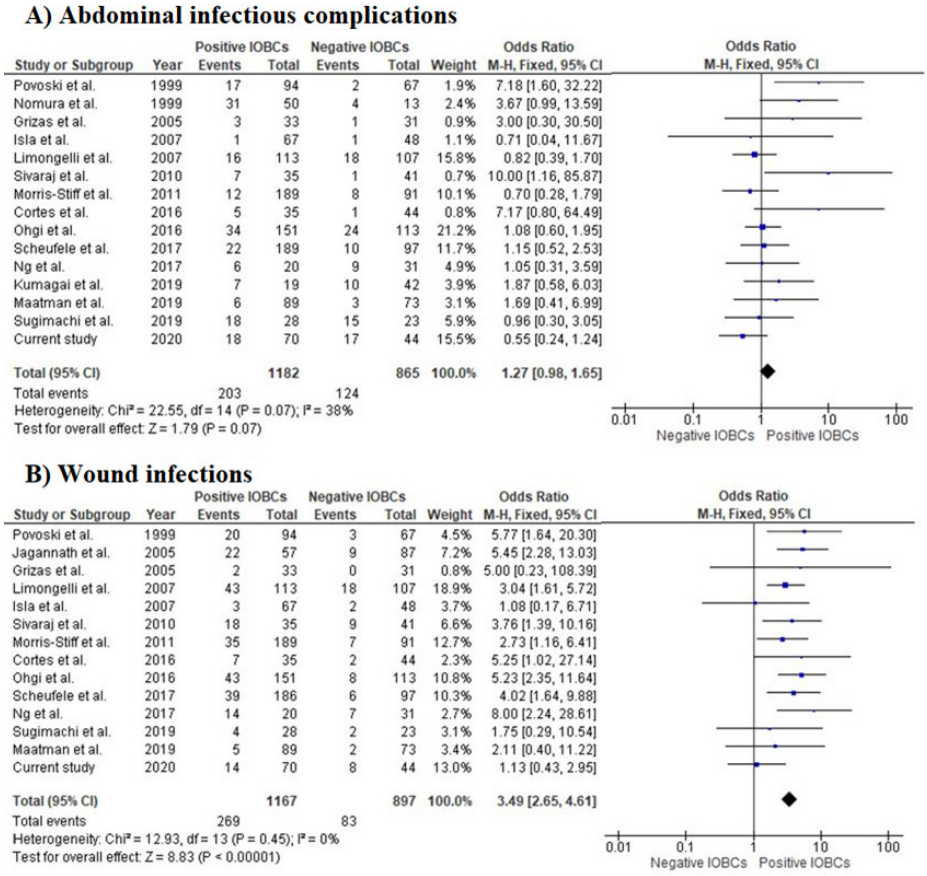

Figure 3. Forest plots for abdominal infectious complications (A) and wound infections (B) in patients with positive versus negative intraoperative bile cultures

DISCUSSION

The primary aim of this study was to evaluate the predictive role of IOBCs in the occurrence of abdominal infectious complications in patients undergoing pancreatoduodenectomy. Positive IOBCs were not associated with the occurrence of OSIs, which was confirmed by the meta-analysis on abdominal infectious complications. Even more, only 8% of patients developed an isolated OSI, which was not associated with IOBC status.

The systematic review and meta-analysis included in this study confirmed the lack of correlation between IOBCs and abdominal infectious complications. Although some studies associated specific microorganisms (e.g. *Enterococcus* and *Enterobacter* species)

with an increased risk for infectious complications, the clinical impact of these findings is questionable.[3, 7, 14, 36, 42] For example, empirical antibiotic therapy is often not directed at *Enterococcus* species.[43, 44] We found a complete concordance of bile and OSI cultures in only one of the nine patients with obtained OSI cultures and OSIs occurring within seven postoperative days. The polymicrobial origin of bile cultures in patients with biliary stents could account for the partial matches, by which the directive value of IOBCs would be negligible. These findings are in line with a recent study also demonstrating a poor concordance between IOBCs and postoperative cultures.[19] Taken together, a positive bile culture seems to be an inadequate predictor for the development of a postoperative infection as well as its causing pathogens.

In this study, the concept of isolated OSI was defined to account for the multifactorial origin of postoperative infections in pancreatic surgery and to rule out interference of confounding complications contaminating the intraabdominal space. Particularly, the occurrence of pancreatic fistula contributes to higher OSI rates as both definitions show considerable overlap. We observed a simultaneous occurrence of pancreatic fistula in 81% of the patients with OSIs. Besides, patients without preoperative biliary drainage generally have a smaller pancreatic duct and a soft pancreatic remnant, which is a risk factor for the development of pancreatic fistula. This is a likely explanation for the observed higher OSI rate in the patients without biliary drainage.[5, 10, 45] Isolated OSIs occurred in only nine patients and OSI rates were similar in patients with positive and negative IOBCs. Whether these low rates are attributable to the prolonged postoperative antibiotic prophylaxis of five days in this study, is subject of further investigation.

The use of postoperative prophylactic antibiotic treatment varies considerably between institutes since evidence for type and duration of postoperative prophylaxis is limited in this type of surgery.[6, 14] In our center, patients received standard antibiotic prophylaxis for five postoperative days. To our knowledge, only one study was conducted to evaluate the effect of prolonged antibiotic prophylaxis after pancreatoduodenectomy. This randomized controlled trial compared one-day to five-days postoperative antibiotic prophylaxis in only patients with preoperative biliary drainage and reported no benefit of prolonged postoperative prophylaxis regarding infectious complications in this group of patients.[46] However, the overall effect of standard prolonged antibiotic prophylaxis after pancreatoduodenectomy remains undetermined. As a more personalized alternative, several retrospective and one randomized controlled trial investigated the value of postoperative antibiotic prophylaxis based on IOBCs or even on preoperative cultures.[4, 5, 47-51] Most studies showed a decrease in wound infections in the IOBC-targeted group, but similar rates of abdominal infectious complications.[4, 48-51] However, type and duration of the antimicrobial prophylaxis varied largely. Also, the selection of the patients receiving the IOBC-targeted or prolonged prophylaxis differed between the studies. Furthermore,

none of these studies used the concept of isolated OSIs and confounding complications could have interfered with the effect of the antibiotic prophylaxis. Altogether, the benefit of IOBC-targeted postoperative antibiotic prophylaxis remains disputable. However, standard use of postoperative antibiotic prophylaxis based on bile cultures will undoubtedly lead to the inappropriate use of broad-spectrum antibiotics.

Given the negligible predictive value of IOBCs and limited evidence for IOBC-based prophylactic antibiotic treatment, routine performance of IOBCs is questionable. Recently, updated recommendations from the Enhanced Recovery After Surgery guidelines stated that bile cultures should only be obtained in patients with biliary drainage and that postoperative antibiotic prophylaxis could be considered in patients with positive IOBCs.[52] The current study confirmed the high incidence of positive IOBCs in patients with a biliary stent. Moreover, performance of a preoperative ERCP without biliary drainage or the presence of periampullary tumors increased the risk of a positive IOBC. For that reason, performance of IOBCs could be considered in these patients if a positive IOBC leads to adequately adjusted postoperative antimicrobial prophylaxis. On the other hand, the high likelihood of a positive IOBC in patients after biliary stenting could be an argument to refrain from obtaining IOBCs, as culture results including specific microorganisms and their resistance patterns will be available after several days, most often coinciding with the end of prophylaxis.

Limitations of this study include the observational designs of the current study and the studies included in the meta-analysis, although results of the qualitative analysis did not change relevantly in a random-effects model. Furthermore, not all 133 consecutive patients were included because of not performed IOBCs, predominantly in patients undergoing robotic surgery. However, baseline characteristics and OSI occurrence of these patients were comparable to the study population. Another limitation is the standard use of postoperative antibiotic prophylaxis, which could have interfered with the development of OSIs. Besides, not all pathogens were identified in positive IOBCs, due to the microbiological assessment by standard laboratory's procedures. Although clinical relevant pathogens were individually evaluated, this factor might have complicated the concordance analysis for which these results were interpreted with a hypothesis-generating intention.

Despite these limitations, this study represents the use of IOBCs in a real-world clinical setting with comparable groups at baseline and clear definitions for OSIs, isolated OSIs and SSIs. Especially the concept of isolated OSI provided insight in the high frequency of confounding complications in patients with abdominal infections after pancreatoduodenectomy. Previous studies used various definitions for infectious complications leading to a disparity in reported abdominal infectious complications. For

instance, Gavazzi et al reported 27% OSIs and 5% abdominal abscesses within the same population.[3] Combined with the systematic review and meta-analysis, an overview of the current knowledge about IOBCs was demonstrated in this study, resulting in a more critical note about the predictive role of IOBCs. With regard to expanding antibiotic resistance and stewardship[53, 54], the current postoperative prophylactic antibiotic treatment should be critically evaluated in a clinical trial to evade unnecessary use of antimicrobial prophylaxis.

In conclusion, similar rates of postoperative infections were observed in patients with positive and negative bile cultures in this study. Regarding the low pathogenicity of the cultured microorganisms and the substantial incidence of confounding non-infectious complications, the predictive value of IOBCs in infectious complications seems limited. Thus, the routine performance of IOBCs should be reconsidered and the efficacy of postoperative prophylactic antibiotic treatment after pancreatoduodenectomy needs further evaluation. The concept of isolated OSI in pancreatic surgery should be incorporated in future studies.

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Supplemental information 1. CDC definition for SSIs and OSIs

Table S1. Center for Disease Control and Prevention's Diagnostic Criteria for Surgical Site Infection (SSI)	
Superficial Incisional SSI	
Criterion	Date of event for infection occurs within 30 days after any NHSN operative procedure. **AND** Involves only skin and subcutaneous tissue of the incision **AND** Patient has at least ***one*** of the following: a) Purulent drainage from the superficial incision. b) Organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiological testing method which is performed for purposes of clinical diagnosis or treatment (for example - not Active Surveillance Culture/Testing (ASC/AST) c) Superficial incision that is deliberately opened by a surgeon - attending physician** or other designee and culture or non-culture based testing is not performed. **AND** Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. d) Diagnosis of a superficial incisional SSI by the surgeon or attending physician** or other designee.
Reporting Instructions for Superficial SSI	**The following do not qualify as criteria for meeting the NHSN definition of superficial SSI** • Diagnosis/treatment of cellulitis (redness/warmth/swelling) - by itself - does not meet criterion "d" for superficial incisional SSI. Conversely - an incision that is draining or that has organisms identified by culture or non-culture based testing is not considered a cellulitis. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration). • A localized stab wound or pin site infection. Such an infection might be considered wither a skin (SKIN) or soft tissue (ST) infection - depending on its depth - but not an SSI. **Note:** A laparoscopic trocar site for an NHSN operative procedure is not considered a stab wound.
Deep Incisional SSI	
Criteria	Date of event for infection occurs within 30 days after the NHSN operative procedure. **AND** Involves deep soft tissue of the incision (for example - fascial and muscle layers) **AND** Patient has at least ***one*** of the following: a) Purulent drainage from the deep incision. b) A deep incision that spontaneously dehisces - or is deliberately opened or aspirated by a surgeon - attending physician** or other designee **AND** Organism is identified by a culture or non-culture based microbiologic testing method which his performed for purposes of clinical diagnosis or treatment (for example - not Active Surveillance Culture/Testing (ASC/AST) or culture or non-culture based microbiologic testing method is not performed **AND** Patient has at least ***one*** of the following signs or symptoms: • Fever (>38.0°C) • Localized pain or tenderness **Note:** A culture or non-culture based test that has a negative finding does not meet this criterion. c) An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam - or imaging test.
**The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s) - infectious disease - other physician on the case - emergency physician or physician's designee (nurse practitioner or physician's assistant). SSI denotes surgical site infection - NHSN denotes the National Healthcare Safety Network	

Supplemental information 1. CDC definition for SSIs and OSIs

"Organ/space SSIs must meet the following criteria:

- Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place *and*
- The infection appears to be related to the operative procedure and infection involves any part of the anatomy (e.g., organs or spaces) other than the incision opened or manipulated during the operative procedure, and at least one of the following is present:
    - 1. Purulent drainage from a drain that is placed through a stab wound* into the organ/space.
    - 2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
    - 3. An abscess or other evidence of infection involving the organ/space on direct examination, during reoperation, or by histopathologic or radiologic examination.
    - 4. Diagnosis of an organ/space SSI by a surgeon or attending physician."

Supplemental information 2. Literature search for PubMed

Combined search of two components (pancreatoduodenectomy and bile cultures): ((((“Pancreaticoduodenectomy”[Mesh] OR “pancreaticoduodenectomy”[tw] OR pancreaticoduodenectom*[tw] OR “pancreatoduodenectomy”[tw] OR pancreatoduodenectom*[tw] OR “duodenopancreatectomy”[tw] OR duodenopancreatectom*[tw] OR “pancreatico duodenectomy”[tw] OR pancreatico duodenect*[tw] OR “duodeno pancreatectomy”[tw] OR duodeno pancreatectom*[tw]) AND (“bile cultures”[tw] OR “bile culture”[tw] OR “bile duct cultures”[tw] OR “bile duct culture”[tw] OR “cultured bile”[tw] OR “bile analysis”[tw] OR “bile analyses”[tw])) OR (“Pancreaticoduodenectomy”[Mesh] OR “pancreaticoduodenectomy”[tw] OR pancreaticoduodenectom*[tw] OR “pancreatoduodenectomy”[tw] OR pancreatoduodenectom*[tw] OR “duodenopancreatectomy”[tw] OR duodenopancreatectom*[tw] OR “pancreatico duodenectomy”[tw] OR pancreatico duodenect*[tw] OR “duodeno pancreatectomy”[tw] OR duodeno pancreatectom*[tw]) AND (“Bile/analysis”[Mesh] OR “Bile/microbiology”[Mesh] OR “biliary stenting”[tw] OR “biliary stents”[tw] OR “biliary stenting”[tw] OR “bile duct stent”[tw] OR “bile duct stents”[tw] OR “bile duct stenting”[tw] OR “biliary duct stent”[tw] OR “biliary duct stents”[tw] OR “biliary duct stenting”[tw])) OR ((“Pancreatectomy”[Mesh] OR “pancreatectomy”[tw] OR pancreatectom*[tw] OR whipple procedure*[tw] OR whipple resect*[tw] OR whipple surger*[tw] OR “bile contamination”[tw] OR bile contamin*[tw] OR “Pancreatic Diseases/surgery”[Mesh] OR pancreatic surg*[tw] OR pancreas surg*[tw]) AND (“bile cultures”[tw] OR “bile culture”[tw] OR “bile duct cultures”[tw] OR “bile duct culture”[tw] OR “cultured bile”[tw] OR “bile analysis”[tw] OR “bile analyses”[tw] OR “biliary stenting”[tw] OR “biliary stents”[tw] OR “biliary stenting”[tw] OR “bile duct stent”[tw] OR “bile duct stents”[tw] OR “bile duct stenting”[tw] OR “biliary duct stent”[tw] OR “biliary duct stents”[tw] OR “biliary duct stenting”[tw]))) AND (english[la] OR dutch[la]) NOT ((“Case Reports”[ptyp] OR “case report”[ti] OR “Review”[ptyp] OR “review”[ti]) NOT (“Clinical Study”[ptyp] OR “trial”[ti] OR “RCT”[ti]))

Supplemental information 3. Study Characteristics

Result: 526 articles in six databases (10 Jan 2020)

						Number of patients (%)		Number of patients (%)		Included outcomes for quantitative analysis	
	Design	Country	Center	Inclusion period	MMB co-authors	Positive IOBCs	Negative IOBCs	Biliary drainage	No biliary drainage	SSIs or wound infections	Abdominal infectious complications
Current study	Prospective	NL	Single	2016-2019	X	70 (61)	44 (39)	59 (44)	74 (56)	X	X
Maxwell *et al.*[19]*	Retrospective	USA	Single	2014-2018		275 (90)	32 (10)	214 (41)	308 (59)		
Kumagai *et al.*[35]	Retrospective	Japan	Single	2015-2017		19 (31)	42 (69)	25 (41)	36 (59)		X
Sugimachi *et al.*[41]	Retrospective	Japan	Single	2014-2017		28 (55)	23 (45)	34 (49)	35 (51)	X	X
Maatman *et al.*[36]	Retrospective	USA	Single	2015-2017	X	89 (55)	73 (45)	89 (55)	73 (45)	X	X
Scheufele *et al.*[39]	Retrospective	Germany	Single	2007-2015		189 (65)	101 (35)	172 (59)	118 (41)	X	X
Ng *et al.*[7]	Retrospective	Australia	Single	2011-2015		20 (83)	4 (17)	31 (61)	20 (39)	X	X
Ohgi *et al.*[6]	Retrospective	Japan	Single	2010-2014		151 (57)	113 (43)	144 (55)	120 (45)	X	X
Fong *et al.*[14]*	Retrospective	USA	Multi	2008-2013		-	-	836 (52)	787 (48)		
Morris-Stiff *et al.*[1]	Retrospective	UK	Single	-		189 (68)	91 (33)	118 (42)	162 (58)	X	X
Sivaraj *et al.*[40]	Retrospective	India	Single	2007-2008		35 (46)	41 (54)	20 (26)	56 (74)	X	X
Limongelli *et al.*[9]	Prospective	UK	Single	-		113 (51)	107 (49)	102 (46)	118 (54)	X	X
Isla *et al.*[33]	Retrospective	UK	Single	1997-2002		67 (58)	48 (42)	52 (45)	63 (55)	X	X
Cortes *et al.*[31]	Case-control	France	Single	2002-2003		35 (44)	44 (56)	34 (43)	45 (57)	X	X
Grizas *et al.*[32]	Retrospective	Lithuania	Single	2002-2004		33 (52)	31 (48)	21 (33)	43 (67)	X	X
Jagannath *et al.*[34]	Retrospective	India	Single	1992-2001		57 (40)	87 (60)	74 (51)	70 (49)	X	
Povoski *et al.*[38]	Retrospective	USA	Single	1994-1997	X	94 (58)	67 (42)	125 (78)	36 (22)	X	X
Nomura *et al.*[37]	Retrospective	Japan	Single	1984-1995		50 (79)	13 (21)	-	-		X

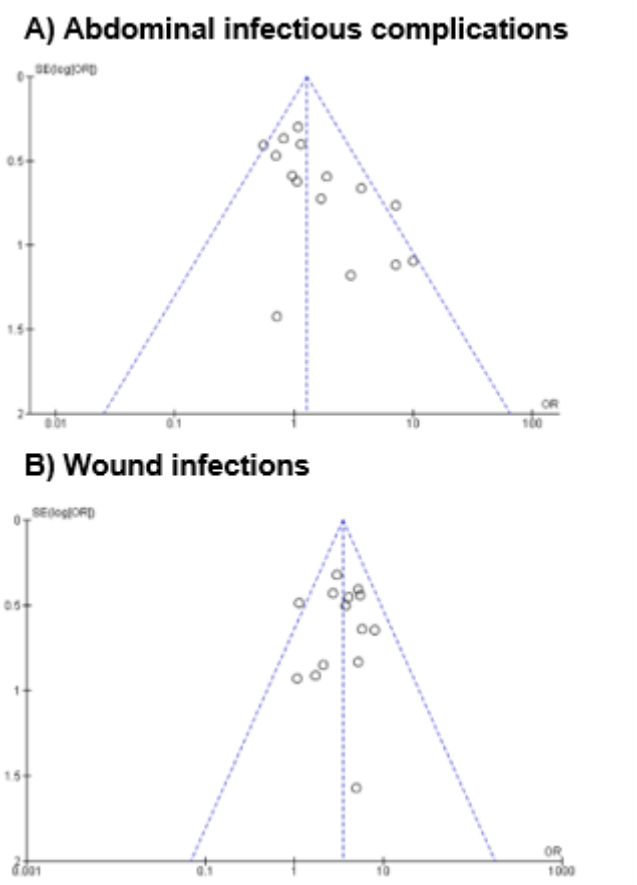
*Studies only included in qualitative analysis.

Supplemental information 4. Risk of bias table according to the ROBINS-1 tool[30]

	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Current study	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Maxwell *et al.*[19]*	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Kumagai *et al.*[35]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Sugimachi *et al.*[41]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Maatman *et al.*[36]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Scheufele *et al.*[39]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Ng *et al.*[7]	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Ohgi *et al.*[6]	Moderate	Low	Low	Low	Low	Serious	Low	Serious
Fong *et al.*[14]*	Moderate	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Morris-Stiff *et al.*[1]	Moderate	Low	Low	Low	Low	Serious	Low	Serious
Sivaraj *et al.*[40]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Limongelli *et al.*[9]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Isla *et al.*[33]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Cortes *et al.*[31]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Grizas *et al.*[32]	Moderate	Low	Low	Low	Serious	Serious	Moderate	Serious
Jagannath *et al.*[34]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Povoski *et al.*[38]	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Nomura *et al.*[37]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate

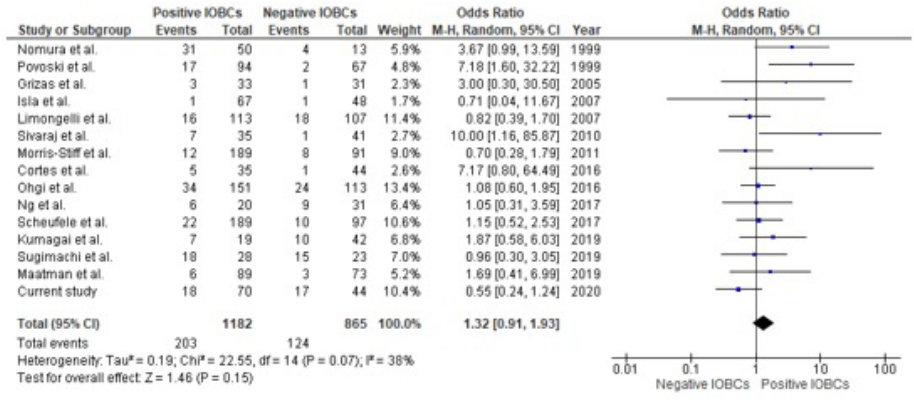
*Studies only included in qualitative analysis.

Supplemental information 5. Funnel plots for abdominal infectious complications (A) and wound infections (B)

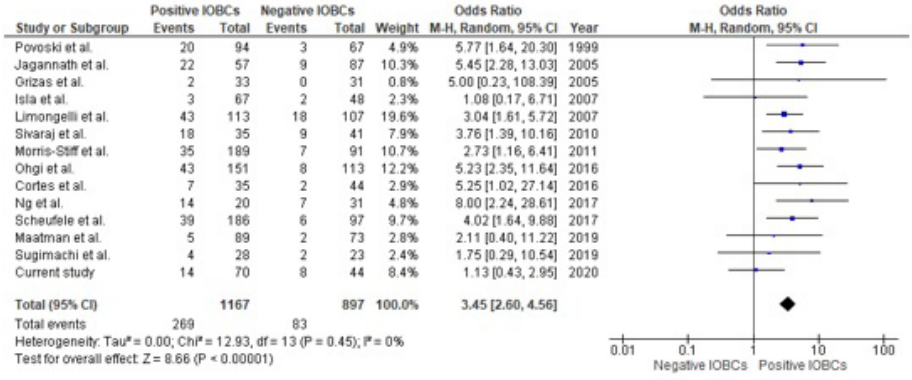


Supplemental material 6. Forest plots for postoperative abdominal infectious complications (A) and wound infections (B) in patients with positive versus negative intraoperative bile cultures, using the random-effects model.

A) Abdominal infectious complications



B) Wound infections



PART IV

PERIOPERATIVE ANESTHESIOLOGICAL MANAGEMENT IN PANCREATIC SURGERY

CHAPTER 12

Epidural and non-epidural analgesia in patients undergoing open pancreatectomy: a retrospective cohort study

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J Gastrointest Surg. 2019 Dec;23(12):2439-2448. doi: 10.1007/s11605-019-04136-w. Epub 2019 Feb 26. PMID: 30809780.

ABSTRACT

Background: The use of epidural analgesia (EA) in pancreatic surgery remains under debate. This study compares patients treated with EA *versus* non-EA after open pancreatectomy in a tertiary referral center.

Methods: All patients undergoing open pancreatectomy from 2013-2017 were retrospectively reviewed. (Non-)EA was terminated on postoperative day (POD) 3 or earlier if required.
Results: In total, 190 (72.5%) patients received EA and 72 (27.5%) patients received non-EA (mostly intravenous morphine). EA was terminated prematurely in 32.6% of patients and non-EA in 10.5% of patients. Compared to non-EA patients, EA patients had significantly lower pain scores on POD 0 (1.10 (0-3.00) *versus* 3.00 (1.67-5.00), P<0.001) and POD 1 (2.00 (0.50-3.41) *versus* 3.00 (2.00-3.80), P=0.001), though significantly higher pain scores on POD 3 (3.00 (2.00-4.00) *versus* 2.33 (1.50-4.00), P<0.001) and POD 4 (2.50 (1.50-3.67) *versus* 2.00 (0.50-3.00), P=0.007). EA patients required more vasoactive medication perioperatively and had higher cumulative fluid balances on POD 1-3. Postoperative complications were similar between groups.

Conclusions: In our cohort, patients with EA experienced significantly lower pain scores in the first PODs compared to non-EA, yet higher pain scores after EA had been terminated. Although EA patients required more vasoactive medication and fluid therapy, the complication rate was similar.

INTRODUCTION

Epidural analgesia (EA) is the current gold standard for perioperative analgesic management in most major abdominal surgeries.[1, 2] However, in patients undergoing pancreatectomy the reported use of EA varies from 10% to 84%.[3-6] The most used alternative for EA is Patient Controlled Analgesia with intravenous morphine (ivPCAM).[3, 5, 7]

Although some studies reported better postoperative pain control in patients with EA compared to other analgesic management options, detailed reports on pain outcomes after pancreatectomy are sparse.[4, 5, 8] In contrast to the generally held belief of the beneficial reported effect of EA on postoperative complications in abdominal surgery,[3, 9, 10] recent studies described adverse effects of EA on postoperative complications, number of Intensive Care Unit (ICU) admissions, and length of hospital stay.[4-7] Furthermore, EA has been associated with perioperative hemodynamic instability and excessive fluid administration, causing early termination of EA, and postoperative complications.[4, 5, 11]

The aim of this study was to compare patients treated with EA *versus* non-EA (N-EA) regarding the analgesic outcomes in the first 10 postoperative days (PODs) and clinical outcomes after open pancreatectomy in our tertiary referral center.

MATERIAL AND METHODS

Study design and patient selection

This retrospective cohort study was approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC), was registered at www.trialregister.nl (TC 6871), and is reported according to the STROBE criteria.[12]

All consecutive patients undergoing pancreatectomy at the LUMC, a tertiary referral center, from June 2013 through December 2017 were reviewed. Analgesic outcomes are structurally registered in the medical records since June 2013, therefore this period was selected. Only patients undergoing open pancreatectomy were included (initial laparotomy and initial laparoscopic procedure converted to laparotomy).

Data collection

Two authors (J.V.G. & D.E.F.S.) performed retrospective data extraction from medical records according to a predefined Case Report Form. Data up to 90 days after surgery or 30 days after discharge were extracted. Extracted data was randomly reviewed by two authors (C.H.M., anesthesiologist & B.A.B., surgeon) for quality control. Variables of

interest included (1) patient related variables: patient characteristics, history of chronic pancreatitis, American Society of Anesthesiologists (ASA)-score, preoperative drug use (opioids, Non-Steroidal Anti-Inflammatory Drugs, oral anticoagulants), underlying pathology, (2) anesthesia-related variables: type- and duration of anesthesia, type- and duration of postoperative analgesic treatment, conversion (*e.g.*, EA to ivPCAM or other analgesia), reason for conversion, type of analgesia following EA or ivPCAM, pain scores, use- and duration of vasoactive support, cumulative fluid balances, (3) surgery-related variables: type- and duration of surgery, blood loss, (4) post-operative variables: duration of admission to the medium care unit (MCU) or ICU, complications related to analgesia treatment, postoperative complications, length of hospital stay, discharge destination, readmission.

Definitions

The EA group consisted of patients with an epidural catheter during surgery and the N-EA group consisted of patients with all types of analgesia other than EA. The day of surgery was considered as POD 0. Pain scores were measured on an 11-point Numerical Rating Scale (NRS) to assess pain intensity: ranging from 0 (no pain) to 10 (most extreme pain imaginable). A NRS > 4 is an indicator for adjustment of the analgesic regimen and was therefore the cut-off value between acceptable and non-acceptable pain and used for analyses of patients who reported unacceptable pain during PODs 0-10.[13] Opioids not part of standard EA or ivPCAM infusion (e.g. intramuscular (IM), subcutaneous (SC), or oral (PO)) were considered 'supplemental opioids'. The reason for EA termination was classified as 'hemodynamic instability' in case perioperative hemodynamic parameters did not improve despite vasoactive medication and fluid therapy. Postoperative pancreatic fistula, post pancreatectomy hemorrhage, bile leakage, delayed gastric emptying, and chyle leak were all classified by the International Study Group of Pancreatic Surgery definitions.[14-18] For all these complications, grade B and grade C were considered as clinically relevant. The following complications of analgesia were investigated: opioid-induced respiratory depression, infection of puncture sites, post-dural puncture headache, and subdural hematoma. The Clavien-Dindo Classification was used to classify overall postoperative complications per patient.[19]

Analgesic management

All patients were preoperatively assessed by an anesthesiologist. Based on the preoperative conditions of the patient, type of surgery, and preferences of both patient and physicians (anesthesiologist and surgeon), a shared decision was made regarding the type of analgesic treatment (*i.e.* EA or N-EA). None of the involved anesthesiologists and surgeons refused to use either EA or N-EA.

Perioperative hemodynamic therapy was goal-directed according to local protocol: focused at maintaining a mean arterial pressure >55 mmHg, a urinary output of >0.5 mL/kg/h and preventing excessive fluid administration.

EA and N-EA treatments were applied according to local protocol. In case of EA, the epidural catheter was inserted preoperatively at level Th6-Th10. EA patients received 0.2% ropivacaine combined with 0.75 μg/mL sufentanil. The background continuous infusion rate was 4-8 mL/h. If needed, patients could manually administer an additional bolus (2 mL, lockout 20 min). In addition, patients received 1 g acetaminophen (paracetamol) 4 times daily. Because of sterility considerations, EA was terminated 72 h after surgery (*i.e.* on POD 3). Thereafter, patients received a combination of acetaminophen and nurse-administered IM / SC / PO opioids (in absence of contra-indications) depending on NRS scores.

Patients with N-EA generally received intravenous (IV) morphine bolus doses postoperatively to reduce pain scores ≤4, followed by ivPCAM. IvPCAM included a background infusion rate of 0.5 mg/h. In addition, the patients could administer a 1 mg bolus at a 5 min interval with a maximum dosage of 28 mg per 4 h. Furthermore, patients received 1 g acetaminophen 4 times daily. IvPCAM was terminated 72 h after surgery (*i.e.* on POD 3). Thereafter, patients continued to receive acetaminophen now combined with nurse-administered IM / SC / PO opioids (in absence of contra-indications) depending on pain scores. The Acute Pain Service[20] was responsible for analgesic management for the duration of EA or ivPCAM. The Acute Pain Service visited the patients twice daily to evaluate and modify analgesic management if needed. Together with the nursing staff, they were responsible for measuring pain scores (on the NRS) at least three times a day according to national protocol.[21]

Outcomes

The primary outcome of this study were the mean pain scores and percentage of patients who reported unacceptable pain per POD. Secondary outcomes were the details of analgesic treatment (percentage, timing and reason of premature termination of initial analgesic technique and use of supplemental opioids), perioperative hemodynamics (vasoactive medication use and cumulative fluid balances) and the postoperative outcomes (postoperative complications- and mortality, and length of hospital stay).

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range) and compared by unpaired *t*-tests or Mann-Whitney U tests, depending on their distribution. Categorical variables are presented as numbers (percentages) and compared by Chi-square or Fisher's Exact tests. For analyses of pain

scores, we calculated the mean NRS per patient per POD and identified patients who reported unacceptable pain (pain score >4) at least once per POD. Because the mean pain scores are not normally distributed, values are presented as median (IQR). Cumulative fluid balances were calculated per patient by adding up fluid balances of preceding days and the POD of interest. Main analyses were based on the comparison of patients with EA *versus* patients with N-EA. Subgroup analyses were performed with patients who completed the first three PODs with their initial analgesic technique (*i.e.* successful EA *versus* successful ivPCAM). For statistical analyses, SPSS Inc. for Windows (version 23.0) was used. *P*-values <0.05 were considered significant.

RESULTS

Patient characteristics and details of analgesic treatment

In total, the study cohort consisted of 262 patients: 190 (72.5%) patients in the EA group and 72 (27.5%) in the N-EA group (Table 1). Both groups were comparable for patient and intraoperative characteristics. However, in the N-EA group, ASA-score, the use of oral anticoagulants and blood loss was higher. In the N-EA group, 64 patients received ivPCAM, six patients received nurse-administered IM / SC / PO opioids, and two patients received a continuous infusion of sufentanil after surgery. Reasons not to use EA were: medical contra-indication (N=28), preoperative failure of placement (N=20), physicians' preference (N=15), and patients' preference (N=9). Type of resection did also not differ between groups (*P*=0.161).

Initial analgesia was terminated on POD 3 without reported problems (according to protocol) in 119 (62.6%) patients with EA and 21 (32.8%) patients with ivPCAM (Figure 1). In 62 (32.6%) patients EA was terminated prematurely due to: inadequate pain control (N=25), hemodynamic instability (N=20), catheter dislocation (N=11), and without reported problems (N=6). In the patients with prematurely terminated EA, 41 patients received ivPCAM following EA (N=6 on POD 0; N=25 on POD 1; N=8 on POD 2; and N=2 on POD 3). In addition, four patients received ivPCAM after termination of EA according to protocol. IvPCAM was terminated prematurely in 16 (10.5%) patients, due to inadequate pain control (N=2) and without reported problems (N=14). All ivPCAM patients received nurse-administered IM / SC / PO opioids after termination of ivPCAM.

Primary outcome

Patients in the EA group had statistically significant lower mean pain scores on POD 0 (1.10 (0-3.00) *versus* 3.00 (1.67-5.00)) and POD 1 (2.00 (0.50-3.41) *versus* 3.00 (2.00-3.80)), whereas they experienced statistically significantly higher mean pain scores on POD 3 (3.00 (2.00-4.00) *versus* 2.33 (1.50-4.00)) and POD 4 (2.50 (1.50-3.67) *versus*

2.00 (0.50-3.00); Figure 2a). From POD 5 forward there were no significant differences between groups.

Table 1. Patient and intraoperative characteristics.

	Type of analgesia		
	EA	N-EA*	
	(N=190 ; 72.5%)	(N=72 ; 27.5%)	*P*
Sex, n (%)			0.688
Male	95 (50.0)	38 (52.8)	
Female	95 (50.0)	34 (47.2)	
Age, mean (SD)	62 (13)	64 (11)	0.395
BMI, mean (SD)	25.3 (4.4)	26.5 (5.2)	0.064
History of chronic pancreatitis n (%)	21 (11.1)	6 (8.3)	0.518
Preoperative opioid use, n (%)	15 (7.9)	10 (13.9)	0.140
Preoperative NSAID use, n (%)	31 (16.3)	9 (12.5)	0.443
Preoperative OAC use, n (%)	8 (4.2)	9 (12.5)	0.015
ASA-score, n (%)			0.024
I	27 (14.2)	6 (8.3)	
II	133 (70.0)	44 (61.1)	
III	30 (15.8)	21 (29.2)	
IV	0	1 (1.4)	
Reason no EA, n (%)			-
Medical contra-indication	-	28 (38.9)	
Preoperative placement failure	-	20 (27.8)	
Physicians' preference	-	15 (20.8)	
Patients' preference	-	9 (12.5)	
Type of anesthesia†, n (%)			0.988
TIVA (propofol)	172 (91.5)	65 (91.5)	
Sevoflurane	16 (8.5)	6 (8.5)	
Type of resection, n (%)			0.161
PPPD / Classic Whipple	142 (74.7)	44 (61.1)	
Total pancreatectomy	12 (6.3)	5 (6.9)	
Distal pancreatectomy	33 (17.4)	20 (27.8)	
Central pancreatectomy	1 (0.5)	2 (2.8)	
Enucleation	2 (1.1)	1 (1.4)	
Laparotomy after conversion‡, n (%)	4 (2.1)	8 (11.1)	<0.001
Blood loss, median (IQR)	800 (450-1225)	1100 (750-1750)	<0.001
Operation time (min), mean (SD)	259 (75)	261 (75)	0.837
Vascular resection§, n (%)	30 (15.8)	6 (8.3)	0.118
Multi-visceral resection¶, n (%)	58 (30.5)	24 (33.3)	0.662

Table 1. Continued

Underlying pathology, n (%)			0.213
Adenocarcinoma	134 (70.5)	45 (62.5)	
Other	56 (29.5)	27 (37.5)	

(N-)EA, (non-)epidural; *SD*, standard deviation; B*MI*, Body Mass Index; *IQR*, interquartile range; *NSIAD*, non-steroidal anti-inflammatory drugs; *OAC*, oral anticoagulants ;*ASA*, American Society of Anesthesiologists; *TIVA*, total intravenous anesthesia; *PPPD*, pylorus-preserving pancreaticoduodenectomy

[*] Included patients with intravenous patient-controlled analgesia with morphine, NSIADs, oral/subcutaneous opioids only, sufentanil perfusor

[†] Missing data: two patients in the EA group, one patient in N-EA group

[‡] Considered as conversion during a laparoscopic intended resection (not diagnostic laparoscopy)

[§] Included wedge –and segmental resection of the superior mesenteric vein, portal vein or hepatic artery

[ǧ] Included resections of spleen, liver, stomach, small bowel, colon, adrenals and kidney

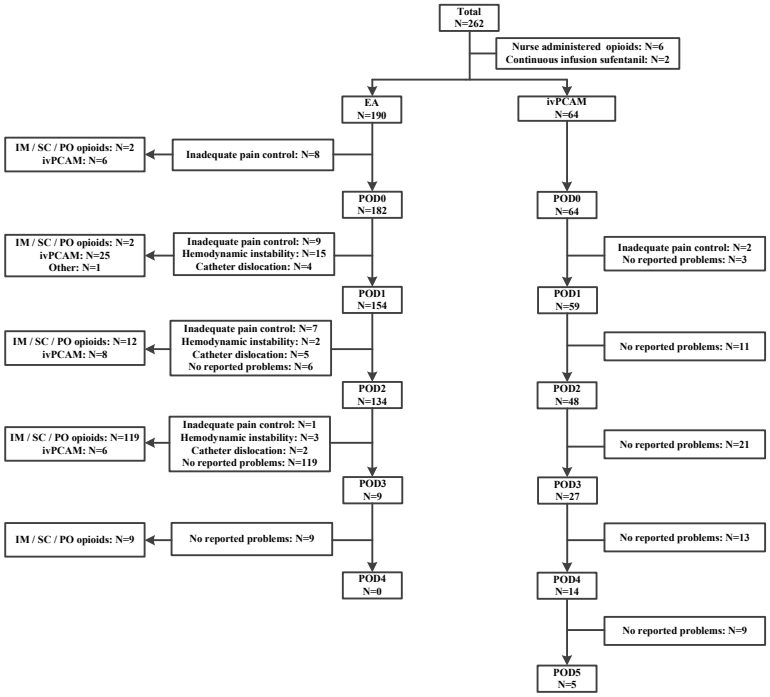

Figure 1. Flow chart of the use of EA and ivPCAM per POD.

The EA group reported unacceptable pain (pain scores >4) significantly less often on POD 0 (31.2% *versus* 63.5%, *P*<0.001; Figure 2b) and POD 1 (31.7% *versus* 49.3%, *P*=0.012). Conversely, the EA-group reported unacceptable pain significantly more often on POD 3 (43.4% *versus* 15.4%, *P*<0.001) and POD 4 (33.1% *versus* 17.7%, *P*=0.023). From POD 5 forward there were no significant differences between groups.

Subgroup analyses showed that EA patients who completed POD 0 (N=182), POD 1 (N=154) and POD 2 (N=134) experienced significantly lower mean pain scores and less unacceptable pain per POD compared to patients with N-EA (Figure S1a-b).

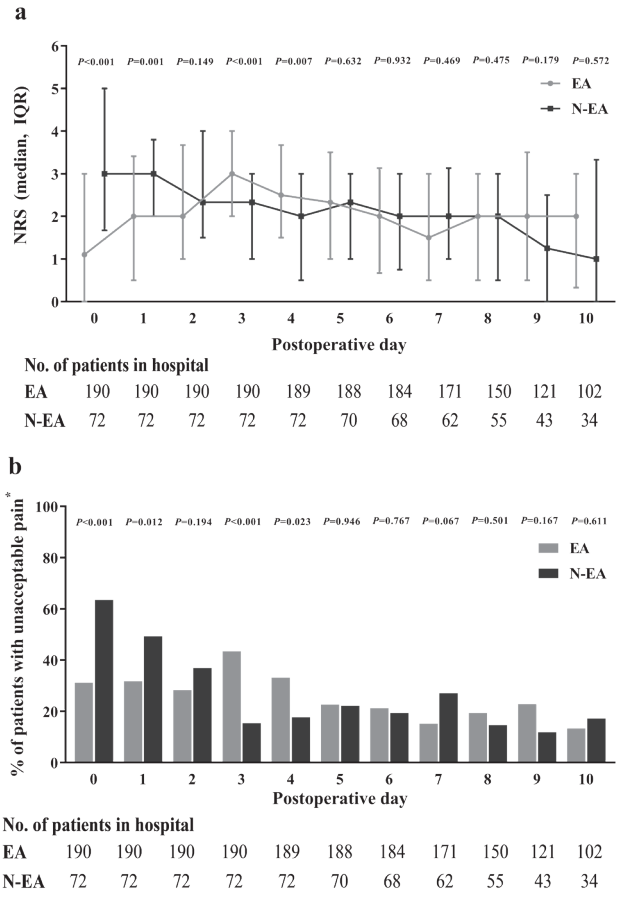

Figure 2. (a) Median (IQR) of mean pain score per POD & (b) Patients with unacceptable pain per POD. * Patients who reported a pain score >4 at least once per POD.

Secondary outcomes

Use of supplemental opioids

More N-EA patients required supplemental opioids to treat their pain on PODs 0-1 (Figure 3). In contrast, on PODs 3-4 significantly more EA patients required supplemental opioids. From POD 5 forward there were no significant differences between groups.

Perioperative hemodynamics

The EA group received more vasoactive medication perioperatively, demonstrated by a significantly higher total dosage of noradrenaline, over a longer period, and with a higher maximum infusion rate (Table 2). Also, the total dosages of phenylephrine and ephedrine were significantly higher in the EA group.

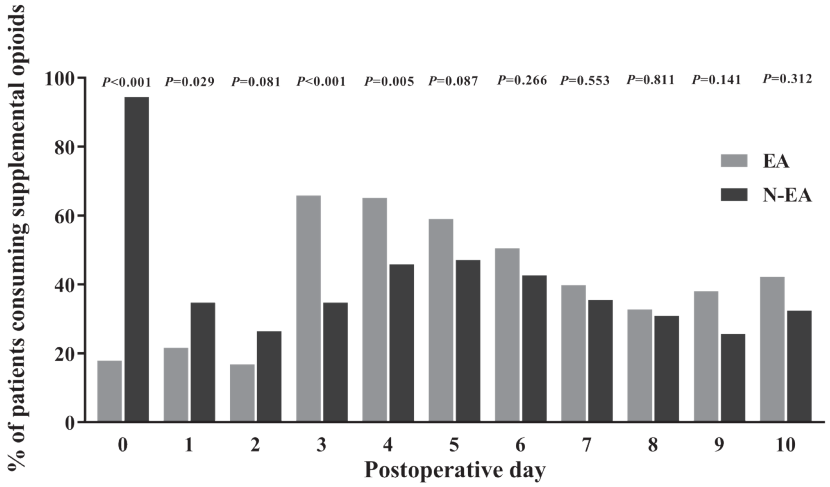

Figure 3. Supplemental opioid consumption per POD.

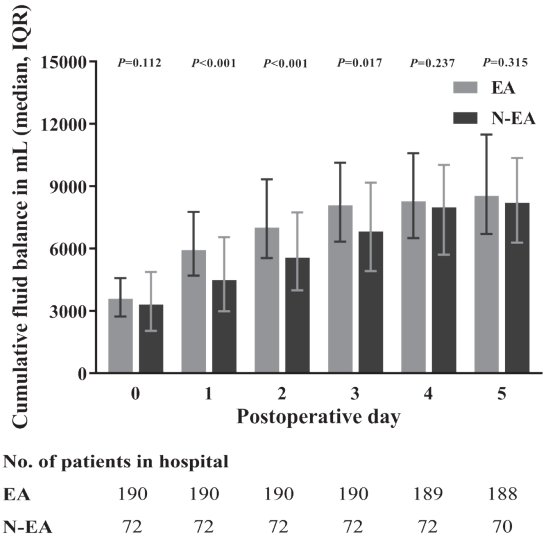

Figure 4. Median (IQR) cumulative fluid balances (mL) per POD.

Both groups had a similar cumulative fluid balance on POD 0 (Figure 4). While on PODs 1-3 the cumulative fluid balance was significantly higher in the EA group (POD1: 5930 (4693-7765) mL *versus* 4485 (2982-6548) mL, *P*<0.001). From POD 4 forward there were no significant differences between groups.

Table 2. Perioperative characteristics.

	Type of analgesia		
	EA	**N-EA***	***P***
	(N=190 ; 72.5%)	**(N=72 ; 27.5%)**	
Duration of anesthesia (min), median (IQR)	301 (257-355)	308 (260-349)	0.740
Intraoperative need of vasoactive medication, n (%)	186 (97.9)	63 (87.5)	<0.001
Noradrenaline, n (%)	152 (80.0)	49 (68.1)	0.041
Phenylephrine, n (%)	145 (76.3)	47 (65.3)	0.071
Ephedrine, n (%)	125 (65.8)	29 (40.3)	<0.001
Postoperative MC/ICU admission, n (%)	168 (88.4)	58 (80.6)	0.099
Duration of postoperative MC/ICU admission (min), median (IQR)	1174 (1055-1325)	1185 (900-1293)	0.157
Postoperative MC/ICU need of vasoactive medication, n (%)	140 (73.7)	31 (43.1)	<0.001
Noradrenaline, n (%)	131 (68.9)	29 (40.3)	<0.001
Phenylephrine, n (%)	19 (10.0)	6 (8.3)	0.682
Ephedrine, n (%)	3 (1.6)	0	0.284
Total dose of noradrenaline (mg), median (IQR)	2.08 (0.45-4.58)	0.64 (0-6.00)	<0.001
Duration of infusion noradrenaline (min), median (IQR)	790 (153-1240)	181 (0-402)	<0.001
Maximum infusion rate noradrenaline µg/kg/min, median (IQR)	0.10 (0.04-0.15)	0.07 (0-0.11)	0.025
Total dose of phenylephrine (µg), median (IQR)	500 (100-1200)	200 (0-700)	0.009
Total dose of ephedrine (mg), median (IQR)	10.0 (0-17.5)	0 (0-10.0)	<0.001

Min, minutes; *IQR,* interquartile range; *MC/ICU,* Medium Care/Intensive Care Unit; mg, milligram; *ug*, microgram; *kg*, kilogram

* Included patients with intravenous patient-controlled analgesia with morphine, NSIADs, oral/subcutaneous opioids only, sufentanil perfusor

Postoperative outcomes

There were no differences between groups regarding postoperative complications and Clavien-Dindo classification (Table 3). In the EA group, three patients had an opioid-induced respiratory depression (EA was already terminated) on the surgical ward which was treated with naloxon without further clinical consequence. No other complications related to analgesia occurred. In total, 7 (3.7%) patients in the EA group and one (1.4%) patient in the N-EA group deceased within 90-days after surgery (*P*=0.335). In all

deceased patients, the cause was not related to type of analgesia. The length of hospital stay did not differ between the two groups.

Table 3. Postoperative outcomes.

	Type of analgesia		
	EA	**N-EA***	
	(N=190 ; 72.5%)	**(N=72 ; 27.5%)**	***P***
CR-POPF†, n (%)	29 (15.3)	9 (12.5)	0.571
CR-PPH†, n (%)	37 (19.5)	18 (25.0)	0.327
CR-BL†, n (%)	10 (5.3)	2 (2.8)	0.390
CR-DGE†, n (%)	43 (22.6)	18 (25.0)	0.686
CR-CL†, n (%)	5 (2.6)	3 (4.2)	0.519
Woundinfection, n (%)	12 (6.3)	8 (6.9)	0.854
Pneumonia, n (%)	12 (6.3)	4 (5.6)	0.819
Intra-abdominal abscess, n (%)	26 (13.7)	15 (20.8)	0.155
Complications of analgesia, n (%)	3 (1.6)	0	0.284
Reintervention, n (%)	49 (25.8)	16 (22.2)	0.551
Relaparotomy	21 (11.1)	7 (9.7)	0.756
Radiological intervention	42 (22.1)	14 (19.4)	0.639
ICU admission, n (%)	31 (16.3)	9 (12.5)	0.443
Length of ICU admission‡, median (IQR)	3 (1-22)	2 (1-7)	0.564
Clavien-Dindo classification§, n (%)			0.419
No complications	55 (28.9)	26 (36.1)	
I-II	77 (40.5)	29 (40.3)	
III-V	58 (30.5)	17 (23.6)	
Ninety-day mortality, n (%)	7 (3.7)	1 (1.4)	0.335
Length of hospital stay (days), median (IQR)	10 (8-14)	9 (8-15)	0.741
Discharge destination, n (%)			0.354
Home	101 (54.6)	33 (46.5)	
Home + additional care	53 (28.6)	21 (29.6)	
Rehabilitation facility	31 (16.8)	17 (23.9)	
Readmission, n (%)	30 (16.3)	16 (22.5)	0.246

CR, clinically relevant; *POPF*, Postoperative Pancreatic Fistula; *PPH*, Postpancreatectomy Hemorrhage; *BL*, Bile leakage; *DGE*, Delayed Gastric Emptying; *CL*, Chyle leakage; *ICU*, Intensive Care Unit; *IQR*, interquartile range

* Included patients with intravenous patient-controlled analgesia with morphine, NSIADs, IM / SC / PO opioids only, sufentanil perfusor

† As defined and classified by the International Study Group Pancreatic Surgery[15-19]

‡ In case of ICU admission

§ Classified according the Clavien-Dindo classification[20]

DISCUSSION

This study showed EA was used in 72.5% of patients undergoing open pancreatectomy. There were several important outcomes of the comparison between EA and N-EA patients: (1) Initial analgesia was prematurely converted to another form of analgesia in 32.6% of EA patients *versus* 10.5% of N-EA patients; (2) EA patients had lower mean pain scores and fewer reported unacceptable pain on PODs 0-1. However, termination of EA led to higher mean pain scores and more patients reported unacceptable pain on POD 3-4, which led to the need for the liberal administration of supplemental opioids; (3) The EA group received more vasoactive medication perioperatively and also cumulative fluid balances were significantly higher on PODs 1-3; (4) Postoperative complications and length of hospital stay were similar between both groups. Previous studies comparing EA with N-EA reported mixed results regarding pain scores and postoperative complications in relatively small cohorts of patients undergoing PD and major hepatopancreatobiliary (HPB) surgery.[4, 5, 7, 22, 23] A recent randomized controlled trial in patients undergoing major HPB surgery showed improved pain control and similar postoperative outcomes between the EA and ivPCAM group, although only 3% of included patients underwent pancreatectomy.[24] Therefore, our large cohort study of solely patients undergoing pancreatectomy provides insight in the effects of analgesic technique. The forthcoming results of a randomized controlled trial comparing EA *versus* ivPCAM in patients undergoing PD could clarify the influence of analgesic technique on postoperative outcomes.[25]

Possible solutions for the higher pain scores after termination of EA might be extending the EA phase or by a preemptive and more strict analgesic treatment (opioid or non-opioid) during the transition from EA to other analgesia. A prolonged EA phase (PODs 4-6) is already implemented in some other centers.[5, 6, 24, 22, 26] Unlike our study, these studies did not report results after termination of EA. Therefore, it is unclear whether extending the EA phase after POD 3 (and delaying the transition from EA to other analgesia) would lead to lower pain scores and less use of opioids. Moreover, previous and our study showed the association between EA and perioperative hemodynamic instability, leading to early termination in 7%-41% of EA (10.5% in our study).[5-8, 26, 27] The higher cumulative fluid balances on PODs 1-3 in the EA group can be explained by the switch from vasoactive medication at the MC/IC to fluid therapy on the surgical ward to ensure adequate hemodynamic status. We hypothesize that excessive fluid therapy on the surgical ward is needed as long as the EA phase is prolonged. Therefore, we suggest not to extend the EA phase but to apply a multimodal analgesic regimen that covers the increase in pain scores upon EA termination.

The high rate of premature termination of EA and worse pain control with ivPCAM implicate that a new alternative for postoperative analgesia is needed. Alternatives for postoperative analgesia have been investigated in previous studies. One study reported results of continuous wound infiltration compared to EA showing lower pain scores, less opioid side-effects, and less use of vasoactive medication after HPB surgery.[28] A possible disadvantage is that the use of multiple wound catheters and pumps might impede early mobilization of the patient. Another study showed that pain scores after subcostal transversus abdominis plane catheters were comparable with EA in upper abdominal surgery.[29] However, the catheters needed re-siting in 45% of patients. Sublingual sufentanil tablets (SST) have been investigated and showed promising pain scores and safety parameters after open abdominal surgery.[30] SST are rapidly absorbed, causing a minimal delay in pain relief, and because peak concentrations are low, typical opioid side effect occur less frequent.[31] The occurrence of other side effects (e.g. headaches and hypotension) are comparable with other forms of opioid treatment.[32] We started an investigator-initiated, multicenter, randomized controlled trial to compare SST and EA in patients undergoing PD (www.trialregister.nl: TC 7318).

Our study has several limitations. The registration of mild side effects (e.g. nausea, pruritus) of analgesia was not reported in a standardized manner, which did not allow comparisons between groups. Our data indicate that the shared decision (by the anesthesiologist and patient) to determine the postoperative analgesic technique is partly based on patient characteristics: the N-EA group had a higher ASA-score and more oral anticoagulant users. It may well be that comparison of outcomes between EA and N-EA patients are not just related to the analgesia technique but also to patient selection. We performed sensitivity analyses with patients undergoing PD (70.2% of patients) which showed similar results regarding all outcomes (data not shown). Nevertheless, in contrast to previous studies, this study presents a large cohort of open pancreatectomies with detailed data of analgesic management in the first 10 PODs and postoperative outcomes.

CONCLUSION

In our cohort, patients receiving EA after open pancreatectomy had significantly lower pain scores in the first PODs compared to non-EA, yet higher pain scores after EA was terminated. Although EA patients required more vasoactive medication and fluid therapy, postoperative complications were similar between groups.

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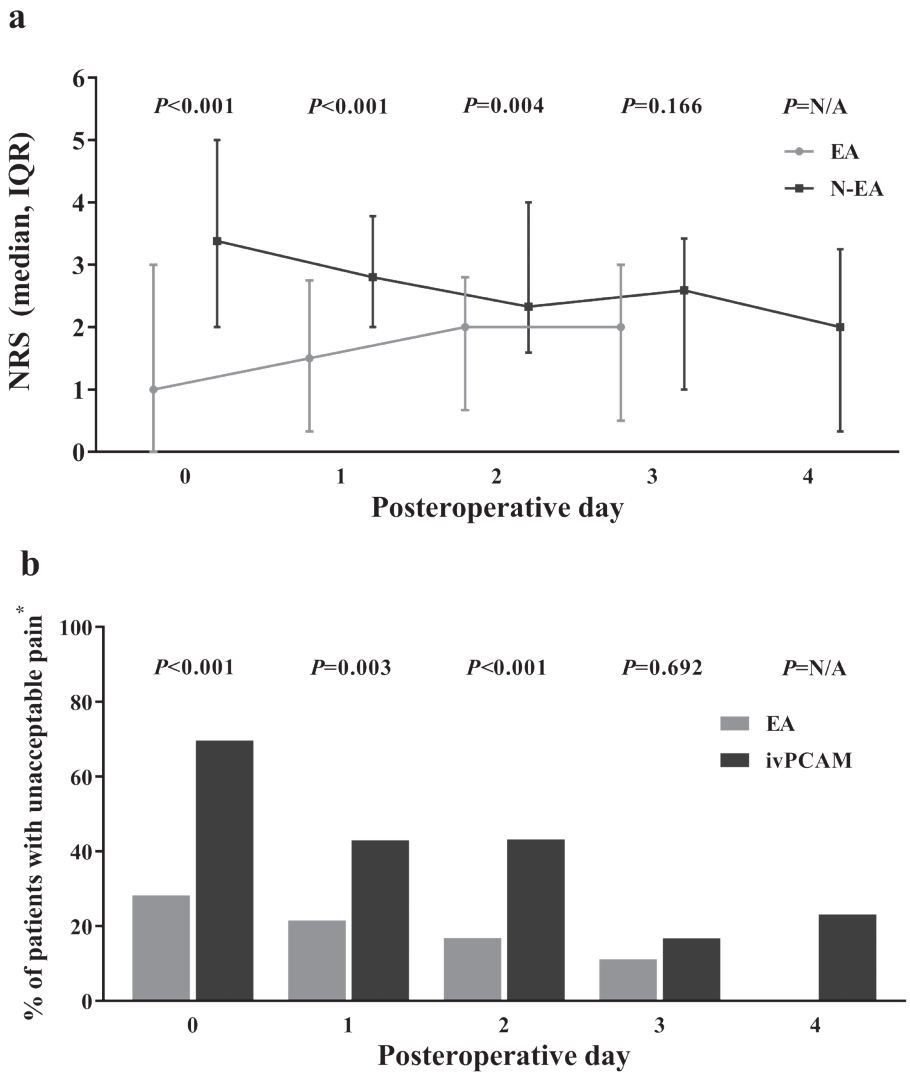
SUPPLEMENTARY MATERIAL



No. of patients with *in situ* EA or ivPCAM					
EA	182	154	134	9	-
ivPCAM	64	59	48	27	14

Figure S1. Subgroup analysis of in situ analgesia: (a) Median (IQR) of mean pain score per POD & (b) Patients with unacceptable pain per POD. * Patients who reported a pain score >4 at least once per POD.

CHAPTER 13

Meta-analysis of epidural analgesia in patients undergoing pancreatoduodenectomy

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ABSTRACT

Background*:* The optimal analgesic technique after pancreatoduodenectomy remains under debate. This study aims to investigate if epidural analgesia (EA) has superior clinical outcomes compared to non-epidural alternatives (N-EA) in patients undergoing pancreatoduodenectomy.

Methods*:* A systematic review and meta-analysis was performed according to the PRISMA guidelines. On 28 August 2018, relevant literature databases were searched. The primary outcomes were pain scores. Secondary outcomes were treatment failure of initial analgesia, complications, length of hospital stay, and mortality.

Results*:* Three randomized controlled trials and eight cohort studies (25 089 patients) were included. N-EA studied were: intravenous (iv) morphine, continuous wound infiltration (CWI), bilateral paravertebral thoracic catheters, and intrathecal morphine. EA patients had a marginally lower pain score over postoperative day 0 to 3 compared with iv morphine (mean difference (MD)=-0·50, 95 per cent confidence interval -0·80 to -0·21; *P*<0·001) and similar pain scores compared with CWI. Treatment failure occurred in 28·5 per cent of EA patients, mainly for hemodynamic instability or inadequate pain control. EA was associated with less complications (odds ratio (OR)=0·69, 0·061 to 0·79; *P*<0·001), shorter length of hospital stay (MD=-2·69 days, -2·76 to -2·62; *P*<0·001) and less mortality compared with iv morphine (OR=0·69, 0·51 to 0·93; *P*=0·01).

Conclusions*:* EA provides marginally lower pain scores in the first postoperative days compared to iv morphine and seems associated with less complications, shorter length of hospital stay, and less mortality. The authors weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy.

INTRODUCTION

Rationale

Patients undergoing pancreatoduodenectomy are at risk of severe postoperative pain due to the incidence of preoperative pain and opioid use, tissue damage and extent of the resection.[1] Epidural analgesia (EA) is the perioperative analgesic technique of choice for most open abdominal surgical procedures and EA has been associated with better pain control after pancreatoduodenectomy.[2-5] Moreover, patients with EA seem to have less pulmonary complications and a lower incidence of postoperative ileus.[6] On the other hand, recent studies described adverse effects of EA on postoperative complications, Intensive Care Unit (ICU) admissions, and length of hospital stay in patients undergoing pancreatoduodenectomy.[3, 5, 7, 8] Furthermore, EA has been associated with hemodynamic instability, and therefore the need for vasoactive medication and excessive fluid administration, which some believe to be associated with impaired anastomotic healing and other complications. [3, 5, 9, 10] EA also bears the risk of technique specific complications e.g. spinal hematoma, epidural abscess, and cauda equina syndrome.[11-13] The heterogeneity in use of EA (ranging 10 to 84 per cent) demonstrates that the ideal perioperative analgesic technique after pancreatoduodenectomy remains under debate.[3, 5, 8, 14]

This systematic review and meta-analysis aims to investigate if epidural analgesia (EA) has superior clinical outcomes compared to non-epidural alternatives (N-EA) in patients undergoing pancreatoduodenectomy by reviewing randomized controlled trials (RCTs) and observational cohort studies.

METHODS

Protocol and registration

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15] and was registered with PROSPERO (registration number: CRD42018085818).

Eligibility criteria

Studies were included if the following predefined inclusion criteria were met: RCTs or observational cohort studies written in English, published between 1 January 1990 and 31 August 2018, reporting >10 patients, comparative study (EA *versus* N-EA), reporting at least one outcome of interest (i.e. it was not mandatory that all outcomes of interest were reported in the study). Studies were excluded if there was no full text available. In

case authors from the same institution published two or more similar studies, the most recent or larger study was included.

Information sources

The Pubmed, Embase, Web of Science and Cochrane library databases were searched for relevant literature. The reference lists of all relevant articles were screened manually and cross-referenced to identify any additional studies. The Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at: www.covidence.org) was used to manage all literature.

Literature search

Two reviewers (J.V.G. & P.A.B.) performed preliminary literature searches for relevant studies. Thereafter, the definite literature search was composed and performed on 28 August 2018 by a librarian using terms as 'pancreatoduodenectomy', 'pancreatic surgery', 'analgesia', 'epidural', and multiple synonyms. The complete literature search available at request.

Study selection

Two independent reviewers (J.V.G. & P.A.B.) screened the titles and abstracts of all obtained articles for the potential to meet the eligibility criteria. Two independent reviewers (J.V.G. & P.A.B.) checked the full texts for the eligibility criteria.

Data collection process & items

A predefined standardized data extraction form was used by two independent reviewers (J.V.G. & A.A.J.K.) to extract study characteristics (study design, nation, inclusion period), patient characteristics (sex, age, American Society of Anesthesiologists (ASA) physical status), analgesic technique protocols, primary and secondary outcomes, and risk of bias. The corresponding authors of included studies were emailed to request additional data on outcomes of interest if outcomes were unclear or not reported.

Outcomes and prioritization

The primary clinical outcomes were pain scores (measured on a 11-point Numerical Rating Scale) during the day of surgery (postoperative day 0) up to postoperative day 3 and the percentage of patients who reported a pain score >4. Secondary clinical outcomes were incidence and reason of treatment failure of initial analgesia, overall complications (reported as: any complication, overall morbidity, all morbidity, any morbidity), specific complications (pneumonia, postoperative pancreatic fistula, ileus), length of hospital stay, and mortality.

Risk of bias

Two independent reviewers (J.V.G. & A.A.J.K.) determined the risk of bias according to the Cochrane Collaboration tool[16] for randomized controlled trials and the ROBINS-I[17] for the cohort studies. Possible publication bias was assessed visually through funnel plots.

Statistical analysis

All analyses were performed using Review Manager (RevMan version 5·3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For description of the study cohorts, continuous variables are presented as mean (standard deviation) and categorical variables are presented as numbers (percentages). When studies did not report mean (standard deviation) of continuous variables, it was estimated using the method described by Wan et al. from the available data (median and (interquartile) range).[18] EA was compared with individual N-EA strategies, by direct comparison of groups. The I^2 statistic was used to assess between study heterogeneity. An I^2 value greater than 50 per cent was considered as evidence for substantial heterogeneity. The number of included studies was limited and cohort sizes varied, therefore the Inverse Variance (continuous outcomes) and Mantel-Haenszel (dichotomous outcomes) fixed effects models were used to calculate pooled effects. Continuous variables are presented as the mean difference (MD) with 95 per cent confidence interval (c.i.) and dichotomous variables are presented as odds ratios (OR) or absolute risk difference with 95 per cent c.i. Two-tailed P <0·050 was considered as statistical significance.

Confidence in evidence

The strength of the evidence and recommendations provided by this systematic review and meta-analysis was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[19]

RESULTS

Study selection and characteristics

The literature search identified 451 unique studies. After screening of titles and abstracts, 36 studies were identified for full-text review (Figure 1). Of these studies, three RCTs[4, 20, 21] and eight cohort studies[3, 5, 7, 14, 22–25] were included. Reasons for exclusion of full-texts are provided in supporting information. The included studies (N=11) described 25 089 patients undergoing pancreatoduodenectomy: 3 010 (12·0 per cent) EA patients and 22 079 (88·0 per cent) N-EA patients. The inclusion period of all studies ranged from 2001 to 2015. Eight studies were conducted in the United Stated of America[3–5, 14, 20, 22, 23, 25], two studies were conducted in Europe[7, 21], and one study was conducted in New Zealand[24] (Table 1). The study cohorts were largely comparable regarding sex, age, (data not shown)

and ASA. Except in the study by Pratt et al.[7] where patients in the N-EA group had a higher ASA.

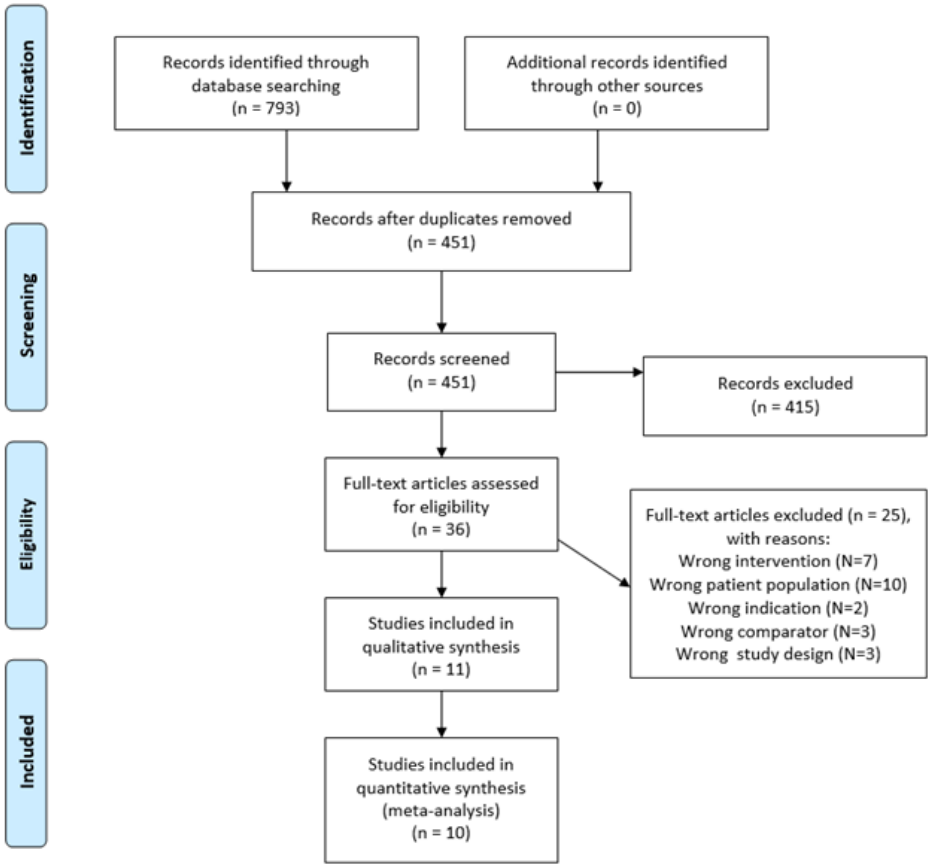

Figure 1. PRISMA flow diagram for the review

The types of EA infusion were: patient-controlled (N=1)[23], continuous infusion (N=5)[4, 5, 7, 20, 25], patient-controlled and continuous infusion (N=1)[21], no information regarding infusion (N=4)[3, 14, 22, 24]. The EA protocols warranted termination between postoperative day 3 and 6 (six studies did not provide information on duration of EA).

The N-EA protocols consisted of intravenous (iv) morphine (N=6)[3-5, 7, 23, 25], continuous wound infiltration (CWI) (N=1)[21], bilateral thoracic paravertebral catheters (BTPC) (N=1)[20], iv morphine and intrathecal morphine (N=1)[24], 'not EA' (N=1)[22], and 'conventional analgesia' (N=1)[14]. In the two studies[14, 22] in which the N-EA protocol was 'not EA'[22] or 'conventional analgesia'[14] it was considered as iv morphine in the meta-analysis, since

Table 1. Study characteristics

	Centre	Country	Inclusion period	No. of patients		ASA grade I-II		Epidural content		N-EA	
				EA	N-EA	EA	N-EA	Infusion	Removal of EA	Type	Removal of N-EA
RCTs											
Marandola *et al.*[4]	Single	USA	2002–2007	16 (40)	24 (60)	14 (88)	20 (83)	CEI	n.s.	i.v. morphine	n.s.
Mungroop *et al.*[21]	Multi	NL	2015	18 (50)	18 (50)	40 (85)*	48 (87)*	PCEA/ CEI	POD 3	CWI	POD 3
Hutchins *et al.*[20]	Multi	USA	2012–2015	23 (48)	25 (52)	0¥	0¥	CEI	POD 4	BTPC	POD 4
Cohort studies											
Pratt *et al.*[5]	Single	USA	2001–2007	185 (79.4)	48 (20.6)	85 (45.9)	13 (27)	CEI	POD 4	i.v. morphine	†
Sakowska *et al.*[24]	Single	NZ	2005–2008	18 (44)	23 (56)	33 (65)*	77 (78)*	n.s.	POD 5	ITM/i.v. morphine	n.s.
Choi and Schoeniger[3]	Single	USA	2004–2007	18 (43)	24 (57)	–	–	n.s.	POD 6	i.v. morphine	POD 6
Amini *et al.*[22]	Multi	USA	2009	947 (11.0)	7663 (89.0)	–	–	n.s.	n.s.	Not EA‡	n.s.
Shah *et al.*[25]	Multi	USA	2007–2011	87 (85.3)	15 (14.7)	18 (21)	3 (20)	CEI	POD 3–5	i.v. morphine	POD 3–5
Patel *et al.*[7]	Single	UK	2006–2009	73 (85)	13 (15)	–	–	CEI	POD 3–4	i.v. morphine	n.s.
Axelrod *et al.*[23]	Single	USA	2007–2011	149 (91.4)	14 (8.6)	–	–	PCEA	n.s.	i.v. morphine	n.s.
Amini *et al.*[14]	Multi	USA	2001–2012	1476 (9.4)	14212 (90.6)	–	–	n.s.	n.s.	Conventional analgesia#	n.s.

Table 2. Risk of bias for RCTs according to the Cochrane Collaboration tool[16]

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessments	Incomplete outcomes data	Selective reporting	Other bias	AHRQ standard*
Marandola *et al.*[4]	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear	Poor
Mungroop *et al.*[21]	Low	Low	High	Low	Low	Low	Low	Fair
Hutchins *et al.*[20]	Low	Low	High	Low	Low	Low	Unclear	Fair

Table 3. Risk of bias for cohort studies according to the ROBINS-I tool[17]

	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Pratt *et al.*[5]	Moderate	Low	Low	Low	Low	Serious	Moderate	Serious
Sakowska *et al.*[24]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Choi and Schoeniger[3]	Serious	Low	Low	Low	Low	Serious	Moderate	Serious
Amini *et al.*[22]	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate
Shah *et al.*[25]	Moderate	Low	Low	Low	Low	Serious	Moderate	Serious
Patel *et al.*[7]	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Axelrod *et al.*[23]	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Amini *et al.*[14]	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate

this is the most used alternative in contemporary literature. A detailed description of analgesic technique protocols is provided in supporting information.

The corresponding author of three studies (Mungroop et al.[21], Shah et al.[25], and Hutchins et al.[20]) provided additional unpublished data at request of the authors.

Risk of bias within studies

The RCT from Marandola et al.[4] was judged as Poor quality, mostly due to unclear quality statements. In the RCTs from Mungroop et al.[21] and Hutchins et al.[20], the domain 'blinding of participants and personnel' was interpreted as high risk of bias and therefore the RCTs were both judged as Fair quality (Table 2). In the cohort studies, mostly the domains 'confounding', 'measurement of outcomes', and 'selection of reported results' were judged as moderate or serious risk of bias, therefore three studies were judged as having a serious[3, 5, 25] and five as a moderate[7, 14, 22-24] overall risk of bias (Table 3).

Primary clinical outcomes

Pain scores on postoperative days 0 to 3

Five studies reported mean pain scores on postoperative day 0 to 3 (435 patients; Figure 2).[4, 5, 7, 21, 25] The mean pain score on postoperative days 0 to 3 was significantly lower in EA compared with iv morphine patients (MD=-0·50, -0·80 to -0·21; P<0·001; Figure 2 (upper)).[4, 5, 25] The analysis of separate postoperative days showed that there was no difference on postoperative day 0 (MD=-0·61, -1·28 to 0·06; P=0·07)[4, 5, 25], but a statistically significant difference on postoperative day 1 (MD=-1·08, -1·66 to -0·50; P<0·001)[4, 5, 25] and postoperative day 2 (MD=-0·66, -1·25 to -0·07; P=0·03) with substantial heterogeneity (I^2=55 per cent; P=0·05)[5, 25], whereas on postoperative days 3 there was no difference (MD=0·16, -0·36 to 0·69; P=0·54)[5, 25]. In addition, Choi et al.[3] reported (42 patients) median pain scores (without interquartile range) and P-values in EA *versus* iv morphine patients and observed no differences: on postoperative day 1 (1·2 *versus* 1·8; P=0·3), postoperative day 2 (1·3 *versus* 2·3; P=0·03), and postoperative day 3 (0·4 *versus* 0·0; P=0·4).

The mean pain score on postoperative days 1 to 3 was similar in EA compared with CWI patients (36 patients; Figure 2 (lower)).[21] Also the analysis of separate postoperative day showed similar mean pain scores.

Hutchins et al.[20] showed (48 patients) no difference in median (range) sum of total maximum pain scores on postoperative days 0 to 4 in EA patients compared with BTPC patients (34·6 (18 to 43) *versus* 30·0 (17 to 51); P=0·364).

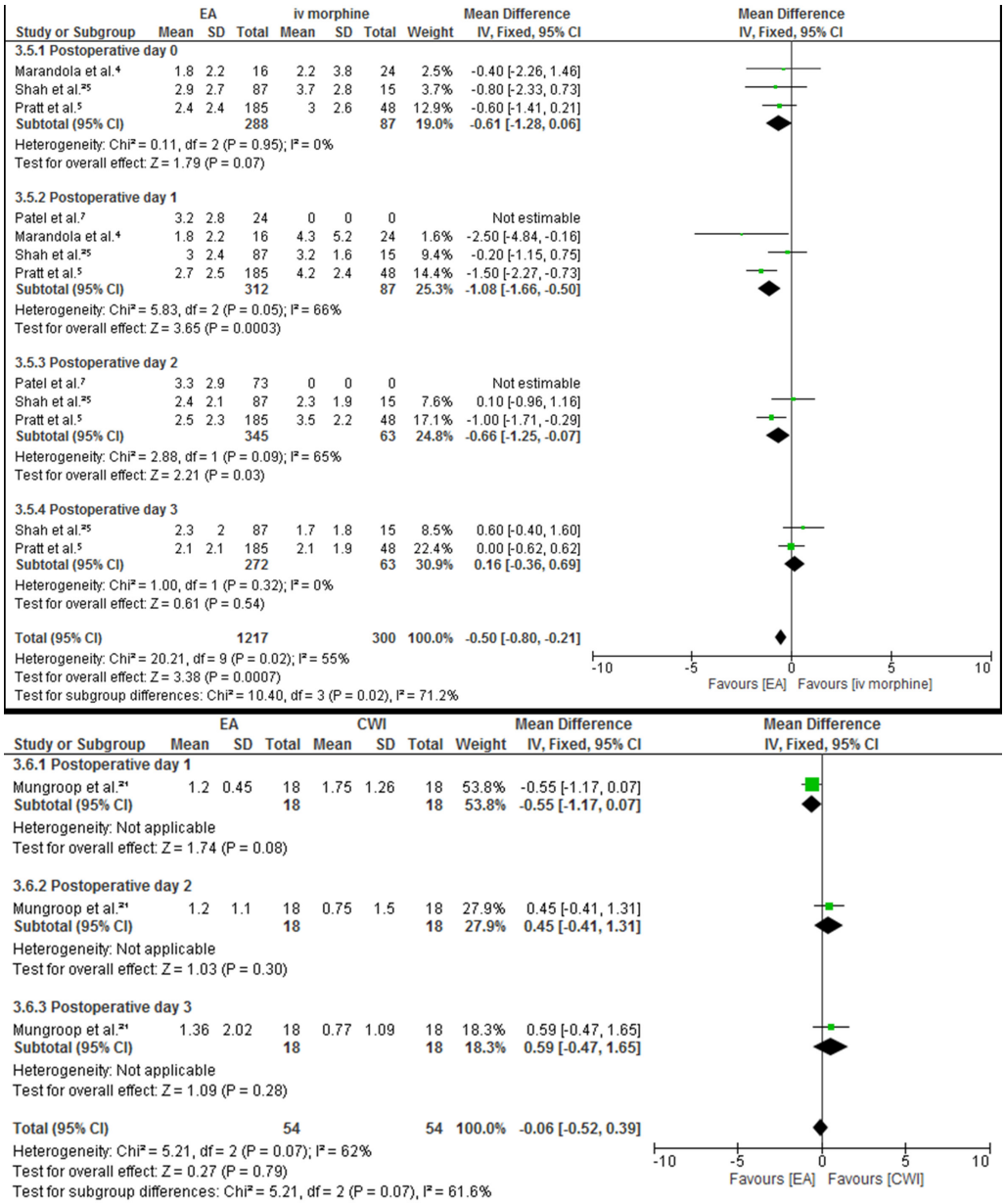

Figure 2. Forest plot of pain scores following treatment with epidural anaesthesia versus non-epidural anaesthesia

Pain scores >4

No studies reported data on this outcome.

Secondary clinical outcomes

Treatment failure of initial analgesia

Four studies reported on treatment failure of EA (425 patients).[3, 5, 7, 23] Overall, treatment failure occurred in 121 (28·5 per cent) EA patients (range between studies: 14·8 to 55·6 per cent). The reason for treatment failure of EA was specified in 111 patients in three studies[5, 7, 23] with the following results: 49 (44·1 per cent) patients due to hemodynamic compromise, 47 (42·3 per cent) patients due to inadequate pain control, and 15 (13·5 per cent) patients due to catheter migration or malfunction.[5, 7, 23] In addition, Hutchins et al.[20] reported that two (8·7 per cent) EA and none BTPC patients required an intervention due to hypotension (unclear if this led to treatment failure).

One study reported on treatment failure of N-EA and this occurred in two (9 per cent) N-EA patients.[3]

Complications

Six studies reported on overall complications (9 150 patients; Figure 3).[3, 5, 21-23, 25] There was a significant difference in overall complications between the EA and iv morphine patients (OR=0·69, 0·061 to 0·79; *P*<0·001)[3, 5, 22, 23, 25] Mungroop et al.[21] showed no difference in overall complications between EA and CWI patients.

There was a significant difference in pneumonia between the EA and iv morphine patients (OR=0·46, 0·33 to 0·63; *P*<0·001; Figure 3)[3, 5, 22, 23] The absolute risk difference in pneumonia between EA (53/1 299=4·1 per cent) and iv morphine (609/7 749=7·9 per cent) patients was -4·2 per cent (-5·5 to -2·9; *P*<0·001).[3, 5, 22, 23]

No significant differences were observed in postoperative pancreatic fistula and ileus between EA and iv morphine patients (Figure 3).[3, 5, 23]

Length of hospital stay

Four studies reported on length of hospital stay (8 928 patients; Figure 4).[5, 20, 22, 24] There was a significant difference in the length of hospital stay between the EA and iv morphine patients (MD=-2·69, -2·76 to -2·62; *P*<0·001) with substantial heterogeneity (I^2=99 per cent; *P*<0·001).[5, 22] Between EA and intrathecal morphine[24] or BTPC patients[20] there was no significant difference.

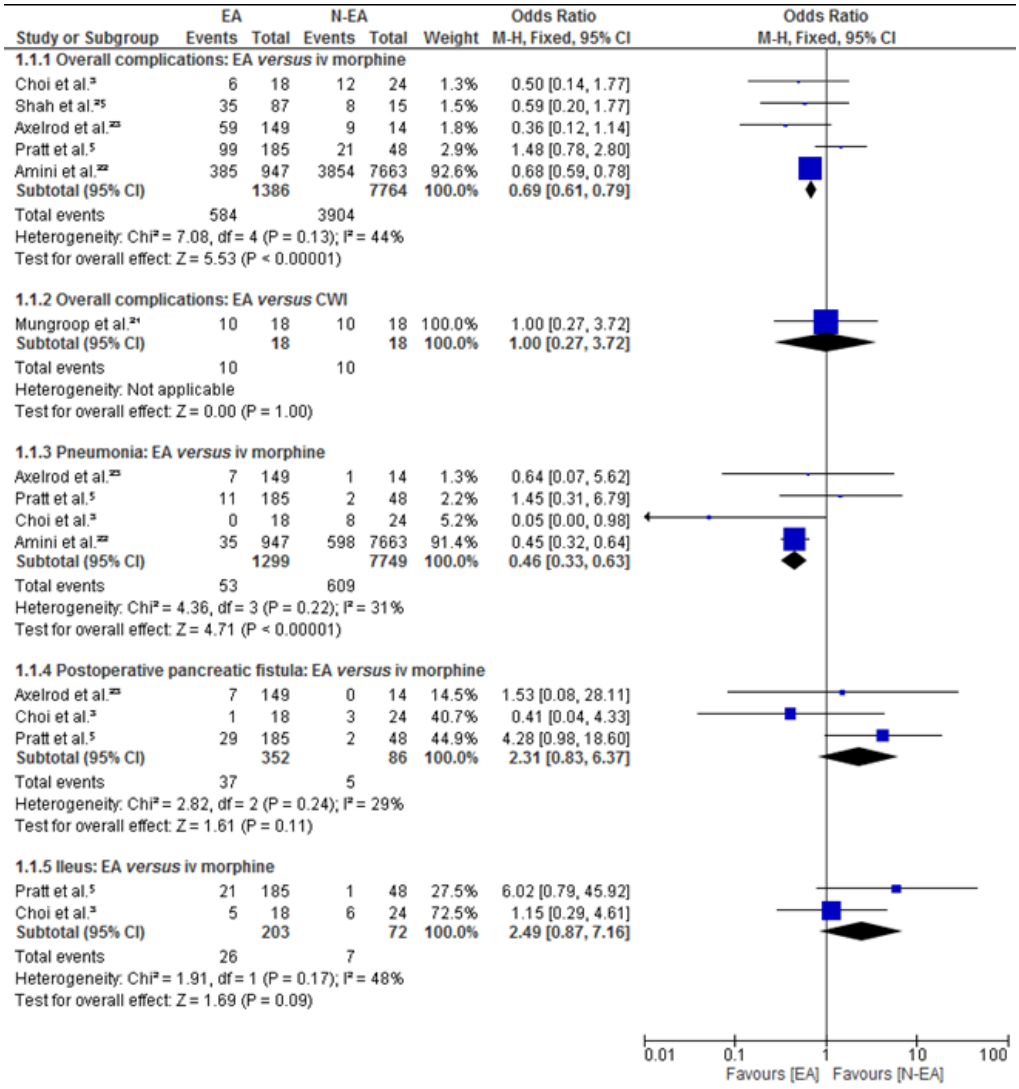

Figure 3. Forest plot of overall complications, pneumonia, postoperative pancreatic fistula and ileus following treatment with epidural anaesthesia versus non-epidural anaesthesia

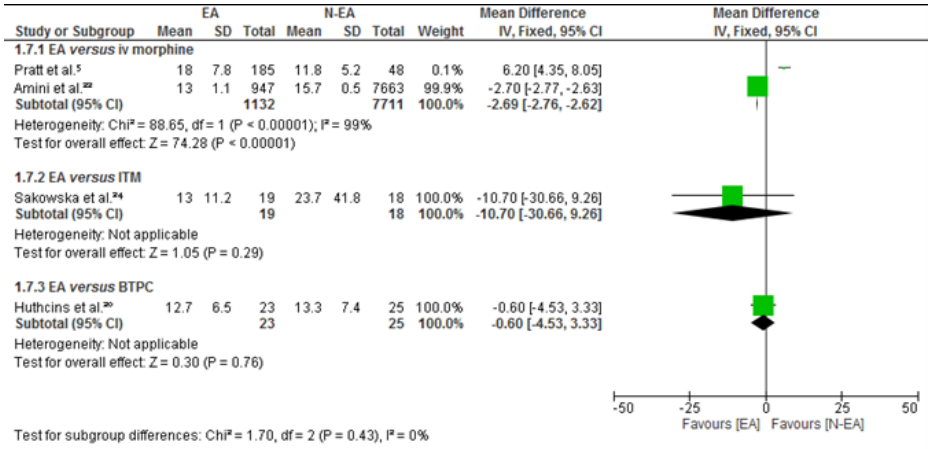

Figure 4. Forest plot of duration of hospital stay following treatment with epidural anaesthesia versus non-epidural anaesthesia

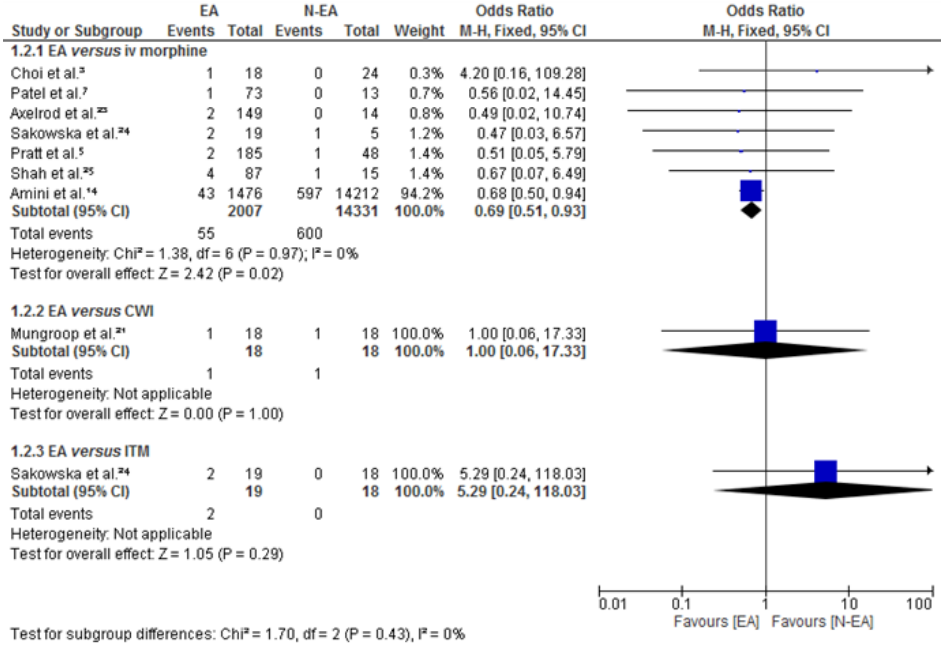

Figure 5. Forest plot of mortality following treatment with epidural anaesthesia versus non-epidural anaesthesia

Mortality

Eight studies reported on mortality (16 392 patients; Figure 5).[3, 5, 7, 14, 21, 23-25] The study from Amini et al.[22] was excluded from this meta-analysis since it was overlapping with the larger study from Amini et al.[14]. There was a significant difference in mortality between EA and iv morphine patients (OR=0·69, 0·51 to 0·93; *P*=0·02). The absolute risk difference in mortality between EA (55/2 007=2·7 per cent) and iv morphine (600/14 331=4·2 per cent) patients was -1·5 per cent (-2 to 0; *P*=0·01).[3, 5, 7, 14, 23-25] Mungroop et al.[21] (EA *versus* CWI) and Sakowska et al.[24] (EA *versus* intrathecal morphine) showed no differences in mortality.

Risk of bias across studies

The funnel plots showed a nearly symmetrical scatter around the mean for all outcomes (Figure 6).

DISCUSSION

This systematic review and meta-analysis of analgesic techniques in patients undergoing pancreatoduodenectomy has several important outcomes. EA provided marginally lower pain scores on postoperative day 0 to 3 compared with iv morphine patients. Results of separate postoperative days showed lower pain scores in EA patients on postoperative days 1 and 2 compared with iv morphine. Treatment failure of EA occurred in 28·5 per cent of patients, mainly as a results of hemodynamic instability or inadequate pain control. Furthermore, there could be a benefit of EA over iv morphine regarding complications, pneumonia, length of hospital stay and mortality. The authors weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy. Also this review highlights the lack of evidence there is on analgesic techniques in patients undergoing pancreatoduodenectomy and emphasizes the need for further studies.

Adequate postoperative pain control is of paramount importance because it has been related to less complications and shorter length of hospital stay.[26, 27] The marginal difference in mean pain score (-0·50 on a 11-point Numerical Rating Scale) on postoperative day 0 to 3 between EA and iv morphine patients might be on itself of limited clinical relevance.[28] The largest difference in mean pain score (-1·08) was on postoperative day 1 in favor of EA and might be of more clinical relevance. There was no data available on patients reporting a pain score >4 (transition from mild to moderate pain) which could have been of more clinical relevance.[29] Unfortunately, also the important pain scores during mobilization were not widely reported in the included studies.[30] Furthermore, it is notable that only two studies used patient controlled EA, since patient controlled EA is associated with improved pain scores, patient satisfaction and safety parameters.[31, 32]

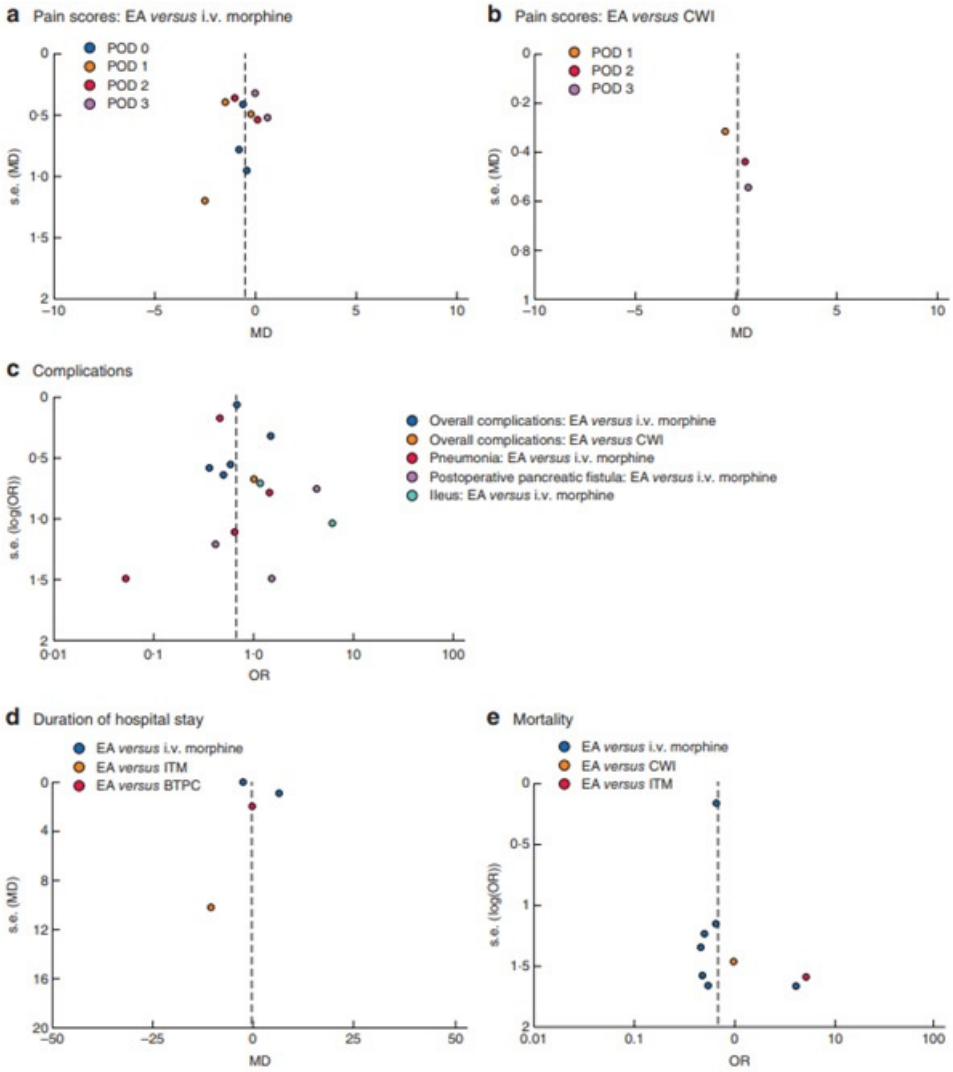

Figure 6. Funnel plots for all outcomes

Nevertheless, in concordance with recent RCTs in major abdominal surgery, the observed differences show that EA has a albeit marginal beneficial effect on pain scores during the first postoperative days compared to iv morphine.[33, 34] The included RCT from Mungroop et al.[21] (EA *versus* CWI) showed non-inferiority regarding pain scores and patient reported outcomes (i.e. Overall Benefit of Analgesia Score) in the subgroup analysis of patients undergoing pancreatoduodenectomy. Furthermore, a recent systematic review and meta-analysis showed improved recovery parameters and patient satisfaction in EA *versus* CWI in abdominal surgery patients and similar pain scores.[35] The included RCT

from Hutchins et al.[20] (EA *versus* BTPC) observed similar maximum pain scores, though this trial was designed to prove a 2-point difference in favor of BTPC.

Less complications occurred in EA compared to iv morphine patients in this study, which is in contrast with previous studies.[33, 34, 36, 37] In this study, solely Amini et al.[22] (EA *versus* iv morphine) reported significantly less complications in EA patients, which remained significant after adjustment for several factors. It remains unclear why results of different studies are contradicting. Treatment failure of EA has been associated with increased postoperative complications and occurred in 28·5 per cent of EA patients in this study.[5, 8, 23] Especially hemodynamic instability as reason for treatment failure is feared, since aggressive fluid therapy may cause pulmonary and anastomotic complications.[5, 23, 38] The authors believe careful patient selection and a dedicated and specialized team (including an Acute Pain Service team[39]) are pivotal for the success of all analgesic techniques.

The observation of a shorter length of hospital stay in EA compared to iv morphine patients was mainly based on the study of Amini et al.[22] conducted in the United States of America. National and hospital health care practices (i.e. discharge criteria) are of major influence on length of hospital stay, one can argue that this beneficial effect of EA on length of hospital stay is not easily generalizable to other clinical settings. A systematic review and meta-analysis of analgesia after abdominal surgery in an Enhanced Recovery After Surgery (ERAS) setting could not prove that EA is associated with a shorter length of hospital stay.[37] This will become more relevant since there is increasing interest in ERAS pathways in pancreatoduodenectomy.[40] Solely the included study from Mungroop et al.[21] specified whether an ERAS setting was used (no data on length of hospital stay). Hence, it cannot be concluded that EA after pancreatoduodenectomy is associated with a shorter length of hospital stay compared to other analgesic techniques.

This meta-analysis showed an absolute risk difference of -1·5 per cent (-2 to 0; P=0·01) on mortality of EA compared to iv morphine. A meta-analysis of RCTs (2 201 patients)[41] and a national cohort study (259 037 patients)[42] in patients undergoing surgery also showed a beneficial effect of EA on mortality, although this benefit disappeared in the subgroup analysis of abdominal surgery patients in both studies. The only included study, Amini et al.[14], that showed lower mortality in EA patients did also perform adjusted analysis for potential confounders in their total cohort (pancreatic and liver resections) in which the beneficial effects of EA remained. As with the outcome overall complications in this study, the influence of residual confounding remains debatable. On the other hand, the analysis of overall complications and mortality showed no significant heterogeneity or publication bias.

This systematic review showed there are only few studies on analgesic techniques after pancreatoduodenectomy. Currently there are two ongoing RCTs: 1) Klotz et al.[43] comparing EA *versus* iv morphine will show whether analgesic technique influences the incidence of complications and mortality after pancreatoduodenectomy and 2) Pak et al.[44] will give insight in the postoperative opioid consumption of EA *versus* iv hydromophone patients after pancreatoduodenectomy. It will be interesting to see how the increasing use of minimally invasive surgery will influence indications for analgesic techniques.[45] Recent studies and experience within the authors region have shown encouraging results and benefits of sublingual sufentanil (non-invasive, rapid absorption and pain relief, and less side effects) over EA and iv morphine.[46-48] Therefore, the authors are conducting a RCT to compare EA *versus* sublingual sufentanil in patients undergoing pancreatoduodenectomy (www.trialregister.nl; TC 7318).

This systematic review and meta-analysis has limitations. The quality of included studies varied. Post-hoc sensitivity analysis without studies of 'Poor quality' and 'serious risk of bias' showed similar results for the secondary outcomes. This could not be performed for the primary outcome (pain scores) since this was the main source of risk of bias due to non-blinding. The studies from Amini et al.[22] (8 610 patients) and Amini et al.[14] (15 688 patients) were large and showed results in favor of EA which mainly determined the secondary outcomes of this meta-analysis. Third, inter-study differences in definitions of the outcomes (treatment failure of initial analgesia, postoperative pancreatic fistula and ileus) might have affected the results. However, the primary outcome (pain scores: all measured on a 11-point Numerical Rating Scale) and other secondary outcomes (overall complications, mortality) are fairly universal in definition. This study pooled data from an RCT (Marandola et al.[4]) and two cohort studies (Pratt et al.[5] and Shah et al.[25]) for estimation of the mean pain scores on postoperative day 0 and 1. This mix of study designs might have introduced heterogeneity. Post-hoc sensitivity analysis showed similar results when analyses were performed separately per study design. And lastly, it is uncertain to what extent the inter-study differences regarding the pain score measurement (e.g. during rest/movement) and analgesic technique (e.g. type and composition of infusion) have influenced the results. To minimize the effect of analgesic technique differences, analysis were performed separately for each type of N-EA.

As a consequence of the risk of bias assessment and mentioned limitations, the evidence should be considered as 'low quality': future studies will have an important impact on the confidence in the evidence and will likely change the evidence. Also, the recommendations should be considered as 'weak': the 'low quality' evidence suggests that desirable and undesirable effects of individual analgesic techniques are in balance (GRADE criteria).[19] Therefore, caution has to be taken when drawing conclusions from this systematic review and meta-analysis.

Strengths of this systematic review and meta-analysis include registration of a predefined protocol, compliance to the PRISMA guidelines, two independent authors who performed the study selection, data extraction and assessment of risk of bias, attempts to contact corresponding authors to provide additional data, and grading of evidence according to the GRADE criteria. This systematic review and meta-analysis summarizes all currently available evidence on EA in patients undergoing pancreatoduodenectomy and analgesic and surgical outcomes.

Clinicians and patients should weigh the possible (marginal) desirable effects of EA (pain scores, complications, length of hospital stay and mortality) with the possible undesirable effects (treatment failure) in every patient, in which patient characteristics such as preoperative pain and opioid use, anticoagulant use and risk of venous thrombosis, cardiopulmonary conditions, inflammatory bowel diseases etc. should all be taken into account.

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SUPPLEMENTARY MATERIAL

Table S1. Reason for exclusion of full texts

Study	Reason for exclusion of full-text
Ahn et al.[1]	Wrong patient population
Aloia et al.[2]	Wrong patient population
Bjersa et al.[3]	Wrong indication
Brandsborg et al.[4]	Wrong intervention
Cyr et al.[5]	Wrong study design
Deng et al.[6]	Wrong intervention
Gastinger et al.[7]	Wrong intervention
Iliescu et al.[8]	Wrong patient population
Klotz et al.[9]	Wrong study design
Lee et al.[10]	Wrong comparator
Min et al.[11]	Wrong comparator
Nakashima et al.[12]	Wrong indication
Niraj et al.[13]	Wrong patient population
Robertson et al.[14]	Wrong patient population
Richardson et al.[15]	Wrong patient population
Rockemann et al.[16]	Wrong intervention
Sanford et al.[17]	Wrong patient population
Seeling et al.[18]	Wrong patient population
Seeling et al.[19]	Wrong patient population
Smith et al.[20]	Wrong study design
Soriano et al.[21]	Wrong intervention
Sugimoto et al.[22]	Wrong comparator
Thompson et al.[23]	Wrong intervention
Wichmann et al.[24]	Wrong intervention
Wu et al.[25]	Wrong patient population

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Table S2. Analgesic treatment protocols

	Epidural content				N-EA				
Reference	**Content**	**Protocol**	**Infusion**	**Removal of EA**	**Type**	**Content**	**Protocol**	**Infusion**	**Removal of N-EA**
Randomized controlled trials									
Marandola et al.[1]	Mepi, ropi, mor	3-mL mepi 20 mg/mL (test), 10-12 mL ropi 7.5 mg/mL + ropi (2 mg/mL) & mor (0.05 mg/mL) at an infusion rate of 5 mL/h.	CEI	NS	iv morphine	Mor	20 mg IV mor in 48 ml saline at 2ml/h	CI	NS
Mungroop et al.[2]	Bupi, sul	PCEA bupi 0·25% & sul 1 µg/mL before incision. Post-op PCEA bupi 0.125% and sul 1 µg/mL at 6 mL/h. CEI bupi 0.125% & sul 0.5 µg/mL at 0.1 mL/kg/h	PCEA/ CEI	POD 3	CWI	Bupi	30 mL bupi 0·25% (at start) + 30 mL bupi 0.25% at 12 mL/h	CWI	POD 3
Hutchins et al.[3]	Bupi, HM	epidural infusion consisted of bupivacaine 0.125% with hydromorphone 6 mcg/mL and was administered via a pump	CEI	POD 4	Paravertebral block	Lido, Epi	1–3 mL of 1.5% lidocaine with epinephrine	CI	POD 4
Cohort studies									
Pratt et al.[4]	Lido, epi, HM, bupi	1.5% lido + epi (test), 8 ml/h HM 20 µg/ml + bupi 0.1% 1mg/ml (n=105) or HM 20 µg/ml + bupi 0.1% 1mg/ml or local bupi 0.1% 1 mg/ml (n=11)	CEI	POD 4	iv morphine	Fen	Fen IV, PCA IV postop	PCA	>
Sakowskaet al.[5]	Ropi en Fen	Ropi 0.2% + Fen 2 µg/ml	NS	POD 5	ITM/iv morphine	Mor, Fen, Bupi	NS	ITM/PCA	NS
Choi et al.[6]	Bupi and HM or Bupi and Fen	(No standard regimen)	NS	POD 6	iv morphine	Mor or HM	(No standard regimen)	PCA	POD 6
Amini et al.[7]	Not specified	NS	NS	NS	Not EA#	NS	NS	NS	NS
Shah et al.[8]	Bupi, mor, HM	0.25% bupi & HM or mor	CEI	POD 3-5	iv morphine	NS	NS	PCA	POD 3–5

Table S2. Continued

Patel et al.[9]	Bupi, Fen, Bupi, PCM	0.1% Bupi and 2 µg/mL Fen, with 10 mL 0.25% Bupi + IV PCM 1 g every 6h	CEI	POD 3-4	iv morphine	Mor, Fen, PCM	0.25 mg/kg IV Mor and 2 µg/kg IV Fen, post-op IV Fen (initially 10-20 µg every 5 minutes IV + IV PCM 1g every 6h	PCA	NS
Axelrod et al.[10]	Bupi, Ropi, Lido, Mor, HM, Fen	0.125% Bupi, 0.2% Ropi or 1% Lido and 0.1 mg/ml Mor, 0.05 mg/ml HM and 10 µg/ml Fen	PCEA	NS	iv morphine	Mor, HM, Fen	0.1 mg/ml Mor, 0.05 mg/ml HM and 10 µg/ml Fen.	PCA	NS
Amini et al.[11]	NS	NS	NS	NS	Conventional analgesia#	NS	NS	NS	NS

Mepi: Mepivacaine, Ropi: Ropivacaine, Mor: morphine, Bupi: bupivacaine, Sul: sulfentanyl, Lido: lidocaine, epi: epinephrine, HM: hydromorphone, Fen: fentanyl, PCM: paracetamol, NS: not specified
#considered as iv morphine for analyses
>Until oral pain medication tolerate

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CHAPTER 14

Sublingual sufentanil versus standard-of-care (patient controlled analgesia with epidural ropivacaine/ sufentanil or intravenous morphine) for postoperative pain following pancreatoduodenectomy: a randomized trial

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ABSTRACT

Background: The optimal treatment strategy for postoperative pain following pancreatoduodenectomy remains unkown. The aim of this study was to investigate whether sublingual sufentanil tablets (SST) is a non-inferior analgesic compared to our standard-of-care (patient controlled epidural analgesia [PCEA] or PCA morphine) in the treatment of pain following pancreatoduodenectomy.

Methods: This was a pragmatic, strategy, open-label, non-inferiority, parallel group, randomized (1:1) trial. The primary outcome was overall mean pain score (Numerical Rating Scale: 0-10) on postoperative day 1 to 3 combined. The non-inferiority margin was -1.5, since this difference was considered clinically relevant.

Results: Between October 2018 and July 2021, 190 patients were assessed for eligibility and 36 patients were included in the final analysis: 17 patients were randomized to SST and 19 patients to standard-of-care. Early treatment failure in the SST group occurred in 2 patients (12%) due to inability to operate the SST system and in 2 patients (12%) due to severe nausea despite antiemetics. Early treatment failure in the standard-of-care group occurred in 2 patients (11%) due to preoperative PCEA placement failure and in 1 patient (5%) due to hemodynamic instability caused by PCEA. The mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI -0.72 – 0.52) and therefore the non-inferiority of SST compared to standard-of-care was demonstrated. The mean pain score, number of patients reporting unacceptable pain (pain score >4), Overall Benefit of Analgesia Score, and patient satisfaction per postoperative day, perioperative hemodynamics and postoperative outcomes did not differ significantly between groups.

Conclusion: This first randomized study investigating the use of SST in 36 patients following pancreatoduodenectomy showed that SST is non-inferior compared to our standard-of-care in the treatment of pain on postoperative day 1 to 3. Future research is needed to confirm that these findings are applicable to other settings.

INTRODUCTION

Epidural analgesia (EA) is the gold standard for perioperative analgesic management in most major open abdominal surgeries.[1] Recently, we performed a systematic review of the various analgesic treatment strategies after pancreatoduodenectomy in our own center[2] and in the current literature[3]. The reported use of EA in patients undergoing pancreatoduodenectomy varies from 9% to 85%.[3] The potential benefits of EA are lower pain scores in the first postoperative days and fewer postoperative (pulmonary) complications.[2, 3] The disadvantages of EA are the invasive nature, early failure rates, hemodynamic instability and notorious, albeit uncommon, complications (eg spinal hematoma and epidural infections).[2-6] The most used alternative for EA is intravenous (iv) morphine.[1-3, 7] The advantages of iv morphine are that most patients are eligible (eg patients with coagulation disorders or spine anatomy alterations) and it is a less invasive method compared to EA. The disadvantages of iv morphine are the suboptimal pain control and a higher consumption of opioids compared to EA with associated side effects.[2, 3, 8] The anesthesia and surgical teams in our center recently concluded that our standard-of-care treatment strategies following pancreatoduodenectomy were currently not comprehensive, and hence alternatives are explored.

Among the available alternatives for EA and iv morphine is sublingual sufentanil tablets (SST). SST consists of a patient-controlled non-invasive hand-held device that delivers 15 µg sufentanil micro-tablets with a 20 min lockout time. The advantages of SST are: (1) it is a non-invasive method of analgesia; (2) sufentanil is highly lipophilic and is rapidly absorbed after which it passes the blood-brain barrier within minutes ($t½\,k_{e0}$ or blood-effect-site equilibration half-life about 6 min); (3) Due to the sublingual formulation peak concentrations are relatively low and consequently, concentration dependent side effects -such as acute respiratory depression- do not occur; and (4) Due to its rapid onset of action, there is little delay in pain relief between the moment of administration and the onset of pain reduction. The disadvantages of SST are the inability to set a background infusion and ability to operate the SST system.[9] SST showed adequate pain control in earlier randomized studies in abdominal and orthopedic surgery and in a recent retrospective cohort analysis of nearly 300 of our patients after laparoscopic abdominal and orthopedic surgery, we observed low average pain scores (75% of patients with a pain score ≤4 on the first postoperative day).[10-13] Nevertheless, no studies are available which investigated the use of SST in patients undergoing pancreatoduodenectomy.[3]

The PROSPECT group states that there might be shortcomings when using general analgesic guidelines for choosing the optimal treatment strategy for postoperative pain following a specific surgical procedure.[14] Therefore, this study compares treatment strategies (rather than medication *per se*) and investigates whether SST is a non-inferior

analgesic compared to our standard-of-care strategy (patient controlled analgesia with EA (PCEA) or patient controlled analgesia with iv morphine (PCA morphine)) in the treatment of postoperative pain following pancreatoduodenectomy.

METHODS

Study design and participants

This was a pragmatic, strategy, open-label, non-inferiority, parallel group, randomized trial in a single center according to the CONSORT guidelines.[15] Inclusion criteria were: American Society of Anesthesiologists score 1 to 3; age ≥18 years; elective pancreatoduodenectomy (eg open or robot-assisted procedures). Exclusion criteria were: unable to give written informed consent; contra-indication for SST, PCEA or PCA morphine such as allergies or coagulopathies; presumed inability to operate the SST or standard-of-care; opioid use >12 weeks; complex chronic pain disorders; liver failure (Child Pugh class C). Patients received information regarding the study preoperatively at the outpatient clinic or by phone. All included patients signed an informed consent form prior to study-related activities. The original protocol and two amendments (also including robot-assisted procedures and changing the non-inferiority margin) were approved by the Medical Ethical Committee (P18.061) and the Board of Directors of the Leiden University Medical Center. A Data Monitoring Committee was deemed not necessary. The full study protocol was registered at Netherlands Trial Register (NTR7318; www.trialregister.nl) and is available at request.

Randomization and blinding

Patients were randomized (1:1) within the electronic data capture system CASTOR (www.castoredc.com), stratified by procedure type (open or robot-assisted; to ensure equal distribution in both groups of the study) and with varying block sizes (4, 6, 8). Patients randomized to standard-of-care received PCEA or PCA morphine at discretion of the attending anesthesiologist and was mainly dependent on procedural type: PCEA for open, PCA morphine for robot-assisted procedures. Blinding of study participants and investigators was not done since the treatment strategies were evidently different.

Treatment strategies

SST

Patients randomized to SST received iv sufentanil during surgery and long-acting iv opioids, such as morphine, 45-60 min prior to the end of surgery. In the Post Anesthesia Care Unit (PACU), pain scores were assessed using an 11-point Numerical Rating Scale (NRS; from 0, no pain to 10, most extreme pain imaginable). If needed, patients received 2 mg iv morphine bolus doses to reduce pain scores ≤4, only when pain scores were ≤4

and patients were able to operate the SST system, the SST system was started. The SST system consists of a patient controlled non-invasive hand-held device that delivers 15 µg sufentanil micro-tablets for sublingual use at a 20 min interval (lockout). An unique adhesive tag on the patients' thumb can activate the device by radio-frequency. The device is fixed to the patients' bed and contains a cartridge with 40 micro-tablets. The Acute Pain Service can manage the SST system with a specific card (remove/replace cartridges, link the thumb tag to the device etc).

Standard-of-care

Patients in the PCEA group received patient controlled epidural analgesia. The PCEA catheter was inserted preoperatively at level Th6-Th10. Following induction of anesthesia, a 6-12 mL bolus containing ropivacaine 0.75% was administered epidurally, followed by a continuous infusion of a mixture of ropivacaine 0.2% and sufentanil 0.75 µg/mL, at 6-10 mL/h; with the possibility of giving an additional bolus. During surgery, patients received additional iv sufentanil if deemed necessary by the attending anesthesiologist. At the PACU, pain scores were assessed at regular intervals and the level of the epidural blockade was tested with an ice pack. In case of pain score >4, 2 mL boluses at a 20 min interval (lockout) from the PCEA system were permitted. In case of failure to place the epidural catheter preoperatively, patients received PCA morphine according to the PCA morphine protocol.

Patients with PCA morphine received patient controlled iv morphine. These patients received 0.1-0.2 mg/kg iv morphine 45-60 min prior to the end of surgery. During surgery, patients received iv sufentanil if deemed necessary by the attending anesthesiologist. At the PACU, pain scores were assessed at regular intervals. If needed, initially, patients received 2 mg iv morphine bolus doses to reduce pain scores ≤4, thereafter the PCA morphine device was started. A background infusion of 0.5 mg morphine per h was administered. Patient could additionally administer a 1 mg bolus at a 5 min intervals (lockout) with a maximum dosage of 28 mg per 4 hours.

Perioperative care

The full study protocol describes the pre, peri and postoperative care in detail and is available at request. All patients received paracetamol 1000 mg 4 times daily and if needed metamizole 1000 mg 3 times daily. In case of insufficient pain treatment (persistent pain scores >4) during the course of treatment, patients could receive rescue pain medication at discretion of the attending anesthesiologist, ie such as conversion to another of the mentioned techniques. If this did not help, iv ketamine could be added (up to 10 mg/h). On postoperative day 3, both the SST system and the standard-of-care were terminated and replaced by paracetamol and oral or subcutaneous (sc) opioids, although both the SST system and the standard-of-care could be prolonged until maximum postoperative day 6 at the discretion of the attending anesthesiologist.

Outcomes and comparisons

There was a single primary outcome, which was the overall mean pain score on postoperative day 1 to 3 combined. The non-inferiority margin was set at -1.5, since a difference greater than -1.5 points was considered to be clinically relevant.[16] Secondary outcomes included mean pain score and patients reporting unacceptable pain per postoperative day, Overall Benefit of Analgesia Score (OBAS)[17] and patient satisfaction score on postoperative day 1 to 3 combined and per postoperative day. Additional secondary outcomes were early treatment failure, perioperative hemodynamics (occurrence of hypotension, use and dosage of vasopressors, postoperative fluid balances) and several additional postoperative outcomes (complications related to analgesia, day of resumption of oral diet intake and day of urinary catheter removal, Clavien-Dindo classification[18], mortality within 30 days, length of hospital stay, readmission).

Outcomes were compared by intention-to-treat analysis (SST *versus* standard-of-care). Predefined subgroup analyses of pain scores were performed by intended procedure type (open and robot-assisted procedure) and protocol version (original and amended protocol). To investigate if older patients had the ability to operate the SST system and achieve adequate pain control, post-hoc subgroup analyses of pain scores were performed by age subgroups of ≤65 and >65 years.

Data collection and definitions

Pain scores were assessed on a 11-point NRS ranging from 0 (no pain) to 10 (most extreme pain imaginable). Pain scores were assessed by the Acute Pain Service (a dedicated and specialized team of nurses and anesthesiologists who visit the patient twice daily and who are responsible for [early] postoperative pain treatment) or nursing staff at least 3 times daily according to local and national protocol.[19, 20] Several training sessions were organized before and during the trial to ensure standardized assessment of pain scores. The OBAS was measured by the Acute Pain Service on the morning on postoperative day 1 to 3. The OBAS is a composite score of pain scores, side-effects, and patient satisfaction, ranging from 0 to 28, in which a lower score is superior to higher scores.[17] Patient satisfaction scores were recorded by the patients themselves at the end of each hospital day (11-point NRS ranging from 0 [not satisfied at al]) to 10 [fully satisfied]). Additional data were collected from the electronic medical records. The day of surgery was considered as postoperative day 0. Perioperative hypotension was defined as a mean arterial pressure <55mmHg. Unacceptable pain was defined as a reported pain score >4. Early treatment failure was defined as ending the use of the SST system or termination of standard-of-care before postoperative day 3 due to problems, such as preoperative placement failure, inadequate pain control, hemodynamic instability, or side effects impeding further treatment. The Clavien-Dindo classification was used to score overall postoperative complications.[18]

Sample size and statistical analysis

Based on a non-inferiority margin of -1.5 for the primary outcome (overall mean pain score for postoperative day 1 to 3 combined), 36 patients were required to be 90% certain that the lower limit of the 95% confidence interval was above the non-inferiority limit (PASS Software version 15.0.4). The primary outcome was tested at the p-value <0.05 level for significance. Mean differences were reported with 95% confidence intervals. In case the confidence interval included the inferiority limit, non-inferiority was considered demonstrated. Further analysis compared groups using independent samples t-test or Mann-Whitney test, depending on their distribution, for continuous variables. Chi-square test and Fisher's exact tests were used for categorical variables. Statistical analyses were performed using the SPSS statistical software package version 26.

RESULTS

Baseline characteristics

Between October 2018 and July 2021, 190 patients were assessed for eligibility of which 38 patients were included (Figure 1). The main reasons for exclusion were temporary stop of study activities in our institution during the peak of the COVID pandemic (n = 40) and logistics (n = 38). Randomization allocated 19 patients in the SST group and 19 patients in the standard-of-care group. Two patients in the SST group were excluded (exclusion criterium found after randomization [n = 1] and no resection being performed [n = 1]) and therefore 36 patients were included in the final analyses.

Baseline characteristics did not differ between the two groups (Table 1). In the SST group, 10 patients (59%) underwent an open procedure, 5 patients (30%) underwent a robot-assisted procedure and 2 (12%) underwent a robot-assisted procedure converted to an open procedure, compared to 11 (58%), 7 (37%) and 1 patients (5%) in the standard-of-care group, respectively (p = 0.739).

In the SST group, early treatment failure occurred in 2 patients (12%) due to the inability to operate the SST system and in 2 other patients (12%) due to severe nausea despite antiemetic treatment (Figure 2). In the standard-of-care group, 10 patients were intended for PCEA and 9 patients were intended for PCA morphine. Early treatment failure occurred in 2 patients (11%) due to preoperative placement failure of PCEA and in 1 patient (5%) due to hemodynamic instability caused by the PCEA. The rate of early treatment failure did not differ between groups (p = 0.558).

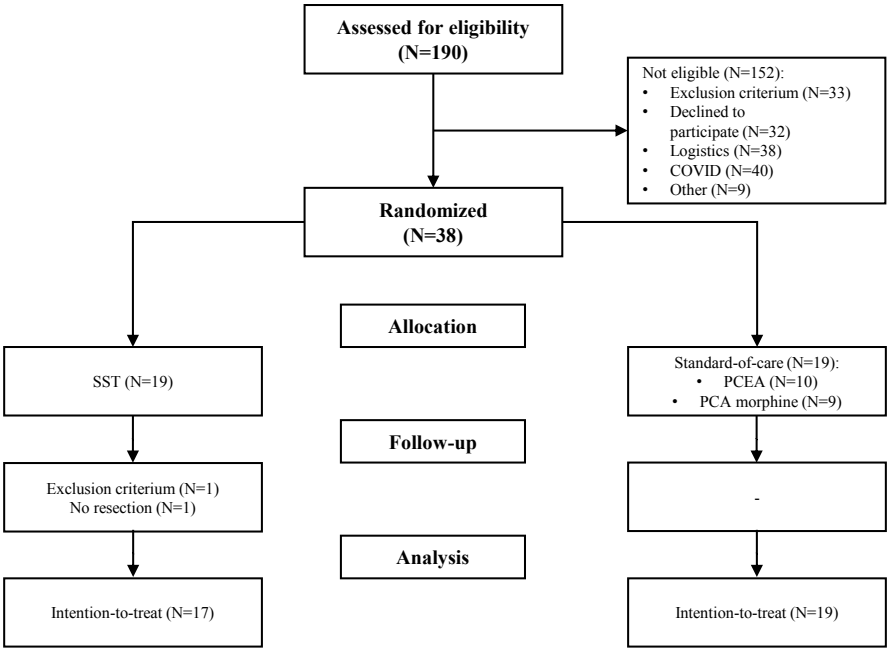

Figure 1. Flow chart of inclusion

Primary outcome

The mean (SD) pain score on postoperative day 1 to 3 was 2.24 (1.00) in the SST group and 2.24 (0.77) in the standard-of-care group. The mean difference was -0.10 (95% CI -0.72 – 0.52) (Table 2). The lower limit of the 95% CI was higher than the predefined limit for non-inferiority (-1.5), and therefore the non-inferiority of SST compared to standard-of-care was demonstrated.

Secondary outcomes

Pain scores

The mean pain score and patients reporting unacceptable pain (pain score >4) per postoperative day did not differ between groups (Table 2; Figure 3). In both groups an increase was observed of patients reporting unacceptable pain on postoperative day 3 compared to day 2.

Overall Benefit of Analgesia Scores (OBAS)

The median (IQR) OBAS on postoperative day 1 to 3 was 7 (3-10) in the SST group and 3 (3-6) in the standard-of-care group (p = 0.126) (Table 2). Also, the median (IQR) OBAS per postoperative day did not differ between groups.

Table 1. Baseline characteristics

		Type of analgesia		
		SST (N=17)	Standard-of-care (N=19)	
		N (%)	N (%)	*P*
Total		**17 (47.2)**	**19 (52.8)**	-
Sex	**Male**	8 (47.1)	14 (73.7)	0.102
	Female	9 (52.9)	5 (26.3)	
Age, median (IQR)		68 (59-74)	63 (57-77)	0.612
BMI, median (IQR)		25.7 (23.3-28.5)	27.7 (23.6-28.4)	0.601
Preoperative acetaminophen use		7 (41.2)	10 (52.6)	0.492
Preoperative NSAID use		0	0	-
Preoperative opioid use		0	2 (10.5)	0.487
ASA-score	**I-II**	11 (64.7)	14 (73.7)	0.559
	III-IV	6 (35.3)	5 (26.3)	
Type of procedure	**Open**	10 (58.8)	11 (57.9)	0.739
	Robot-assisted	5 (29.4)	7 (36.8)	
	Conversion to open	2 (11.8)	1 (5.3)	
Type of incision	**Midline**	12 (70.6)	12 (63.2)	0.732
	Minimally invasive	5 (29.4)	7 (36.8)	
Type of analgesia	**PCEA**	-	10 (52.6)	-
	PCA morphine	-	9 (47.4)	
Type of resection	**PPPD**	10 (58.8)	12 (63.2)	0.790
	Classic Whipple	7 (41.2)	7 (36.8)	

SST, sublingual sufentanil tablets; *IQR,* interquartile range*; BMI*, Body Mass Index; *NSIAD*, non-steroidal anti-inflammatory drugs*; ASA,* American Society of Anesthesiologists*; PCEA,* patient controlled epidural analgesia; *PCA morphine*, patient controlled analgesia with morphine; *PPPD,* pylorus-preserving pancreaticoduodenectomy

Patient satisfaction scores

The median (IQR) patient satisfaction score on postoperative day 1 to 3 was 7 (5-9) in the SST group and 8 (7-9) in the standard-of-care group (p = 0.337) (Table 2). Median (IQR) patient satisfaction scores per postoperative day did not differ between groups.

Perioperative hemodynamics

Perioperative characteristics did not differ between groups (Table 3). The use and total dosage of vasopressors did not differ between groups. In the SST group, 7 patients (41%) experienced perioperative hypotension compared to 5 patients (26%) in the standard-of-care group (P = 0.345). Fluid balances on postoperative day 0 to 5 did not differ between groups.

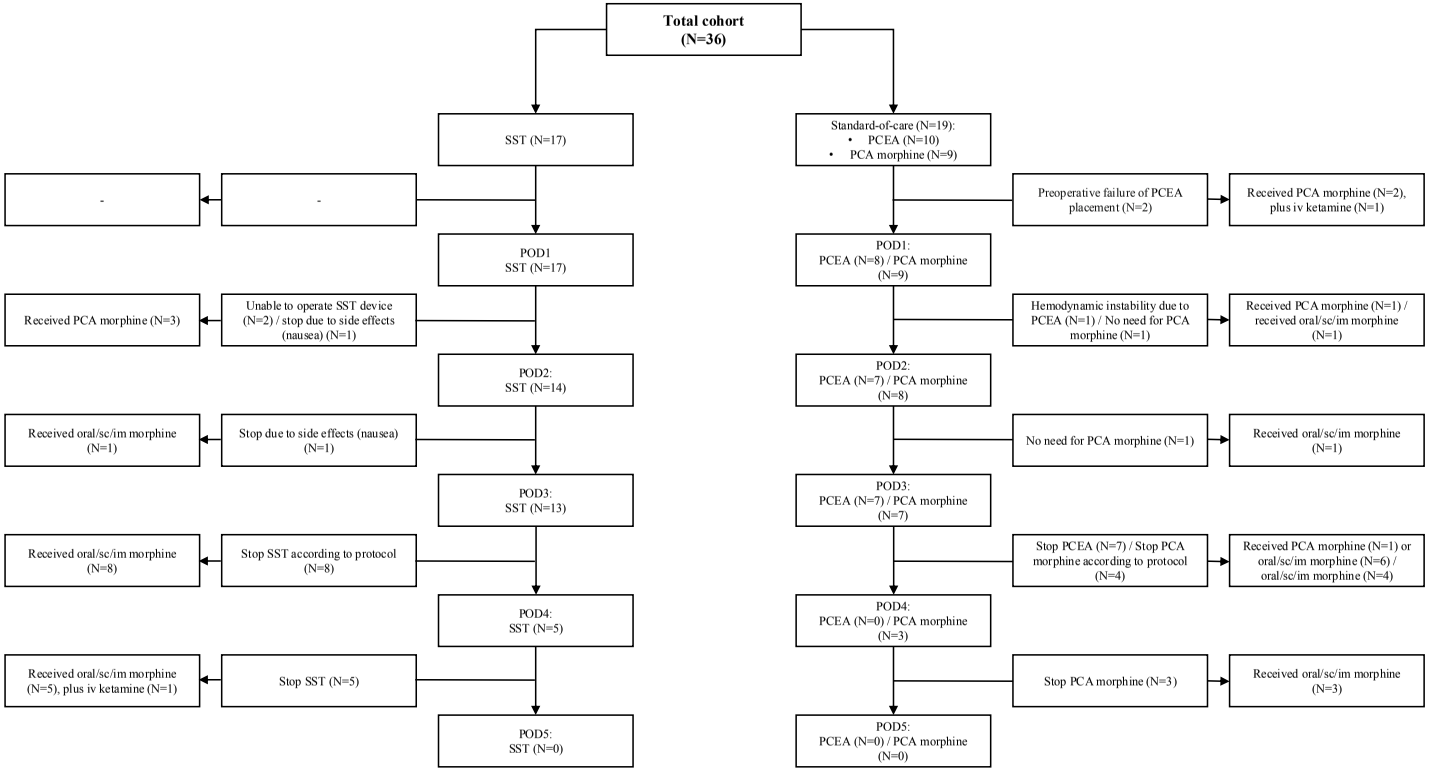

Figure 2. Flow chart of the use of SST and standard-of-care per postoperative day

Table 2. Mean difference in pain scores, Overall Benefit of Analgesia Score (OBAS) and patient satisfaction scores per postoperative day

	Type of analgesia		
	SST (N=17)	Standard-of-care (N=19)	
	Mean differences (95% CI)		*P*
Pain score POD 1 to 3	-0.10 (-0.72 – 0.52)		0.738
Pain score POD 0	-0.03 (-1.42 – 1.37)		0.969
Pain score POD 1	0.17 (-0.60 – 0.94)		0.658
Pain score POD 2	0.17 (-0.70 – 1.04)		0.688
Pain score POD 3	-0.50 (-1.44 – 0.45)		0.293
Pain score POD 4	- 0.24 (-1.12 – 0.64)		0.585
Pain score POD 5	-0.51 (-1.52 – 0.50)		0.309
	Median (IQR)	**Median (IQR)**	***P***
OBAS POD 1 to 3	7 (3-10)	3 (3-6)	0.126
OBAS POD 1	8 (4-9)	3 (2-6)	0.144
OBAS POD 2	5 (1-11)	4 (2-6)	0.762
OBAS POD 3	5 (2-8)	3 (2-5)	0.140
Patient satisfaction POD 1 to 3	7 (5-9)	8 (7-9)	0.337
Patient satisfaction POD 1	6 (1-9)	9 (8-10)	0.105
Patient satisfaction POD 2	8 (5-8)	8 (8-10)	0.050
Patient satisfaction POD 3	8 (6-9)	7 (3-9)	0.609

SST, sublingual sufentanil tablets; *CI,* confidence interval; *POD*, postoperative day; *OBAS*, Overall Benefit of Analgesia Score, *IQR,* interquartile range*;*

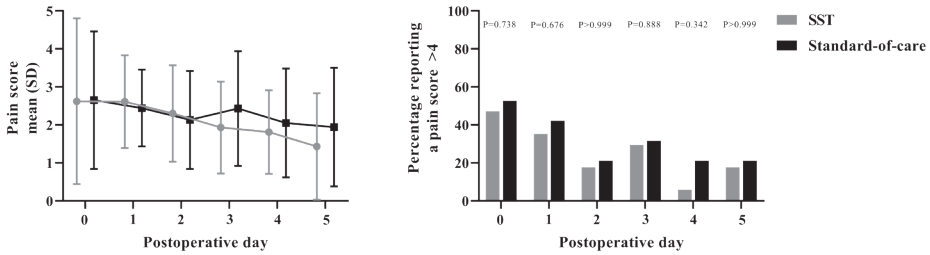

Figure 3. Mean (SD) pain score per postoperative day (left), and percentage of patients reporting a pain score >4 per postoperative day (right)

Additional postoperative outcomes

Postoperative characteristics did not differ between groups (Table 3). In both groups, 1 patient (SST group: 6%, standard-of-care group: 5%) experienced a complication related to analgesia (SST group: respiratory depression with good effect of naloxone treatment, standard-of-care group: hemodynamic instability with good effect of stopping PCEA).

Subgroup analysis

Predefined subgroup analysis by intended type of procedure

Patients undergoing an intended open procedure (SST [*n* = 10] *versus* standard-of-care: PCEA [*n* = 10] and PCA morphine [*n* = 1]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference -0.23 [95% CI -1.22 – 0.75]). The mean (SD) pain score on postoperative day 3 was significantly lower in the SST group compared to the standard-of-care group (1.19 [0.97] *versus* 2.75 [1.84]; p = 0.03). Other pain scores per postoperative day did not differ between these groups. Patients undergoing an intended robot-assisted procedure (SST [*n* = 7] versus standard-of-care: PCA morphine [*n* = 8]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference 0.02 [95% CI -0.58 – 0.62]). The mean (SD) pain score on postoperative day 1 was significantly lower in the SST group compared to the PCA morphine group (2.42 [0.83] *versus* 3.22 [0.44]; p = 0.033). Other pain scores per postoperative day did not differ between these groups.

Predefined subgroup analysis by original and amended protocol

Patients during the original protocol (SST [*n* = 3] versus standard-of-care [*n* = 5]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference 0.98 [95% CI -2.23 – 2.56]). The mean (SD) pain scores on postoperative day 0 and 1 were significantly higher in the SST group compared to the standard-of-care group (3.67 [1.1] versus 1.62 [1.17]; p = 0.05 and 3.83 [1.74] *versus* 1.28 [0.82]; p = 0.027). Other pain scores per postoperative day did not differ between these groups. Patients during the amended protocol (SST [*n* =14] versus standard-of-care [*n* = 14]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference -0.17 [95% CI -0.80 – 0.47]). Pain scores per postoperative day did not differ between these groups.

Post-hoc subgroup analysis by age

Patients ≤65 years (SST [*n* = 8] versus standard-of-care [*n* = 10]) and >65 years (SST [*n* = 9] versus standard-of-care [*n* = 9]) showed similar results for mean pain score on postoperative day 1 to 3 and mean pain score per postoperative day (data not shown).

Table 3. Perioperative hemodynamics and postoperative outcomes

	Type of analgesia		
	SST (N=17)	Standard-of-care (N=19)	
	N (%)	N (%)	*P*
PERIOPERATIVE HEMODYNAMICS			
Intraoperative use of vasopressors	17 (100)	18 (94.7)	1.00
Noradrenaline	16 (94.1)	18 (94.7)	1.00
Phenylephrine	12 (70.6)	11 (57.9)	0.429
Ephedrine	8 (47.1)	10 (52.6)	0.738
Postoperative MC/ICU use of vasopressors	8 (47.1)	10 (52.6)	0.738
Noradrenaline	8 (47.1)	10 (52.6)	0.738
Phenylephrine	0	0	-
Ephedrine	0	2 (10.5)	0.487
Total dose of noradrenaline (mg), median (IQR)*	0.60 (0.28-2.08)	1.08 (0.56-4.76)	0.358
Total dose of phenylephrine (mg), median (IQR)*	150 (0-300)	50 (0-250)	0.359
Total dose of ephedrine (mg), median (IQR)*	0 (0-5.0)	3.0 (0-12.5)	0.243
Cumulative fluid balance			
POD 0 (mL), median (IQR)	2517 (2291-4187)	2625 (1836-3196)	0.522
POD 1 (mL), median (IQR)	3736 (3361-5342)	3590 (3029-6195)	0.968
POD 2 (mL), median (IQR)	4927 (4172-6241)	5601 (4640-7750)	0.262
POD 3 (mL), median (IQR)	6219 (3773-6532)	6397 (4854-7674)	0.137
POD 4 (mL), median (IQR)	6718 (3597-7979)	7369 (5711-8219)	0.233
POD 5 (mL), median (IQR)	7965 (5268-9381)	9015 (6577-9885)	0.233
POSTOPERATIVE OUTCOMES			
Complications related to analgesia**	1 (5.9)	1 (5.3)	0.935
Day of resumption of oral diet intake, median (IQR)***	3 (3-5)	3 (2-5)	0.571
Day of urinary catheter removal, median (IQR)	3 (3-4)	3 (2-4)	0.544
Clavien-Dindo classification			0.357
No complications	11 (64.7)	8 (42.1)	
I-II	1 (5.9)	3 (15.8)	
III-V	5 (29.4)	8 (42.1)	
30-day mortality	0	0	-
Length of hospital stay (days), median (IQR)	9 (7-12)	8 (7-14)	0.778
Readmission	2 (11.8)	6 (31.6)	0.182

IQR, interquartile range*; MC/ICU*, Medium Care/Intensive Care Unit; *mg*, milligram; *IQR*, interquartile range; *POD*, postoperative day;

* Missing data for SST group (N=2)

** In the SST group: respiratory depression, in the standard-of-care group: hemodynamic instability

*** Missing data for SST group (N=1) and standard-of-care group (N=2)

DISCUSSION

This first randomized study investigating the use of SST in 36 patients following pancreato-duodenectomy showed that the SST treatment strategy, as part of a multimodal approach, is a non-inferior analgesic compared to our standard-of-care (PCEA or PCA morphine) in the treatment of pain on postoperative day 1 to 3. Early treatment failure occurred in 24% of patients in the SST group and in 16% of patients in the standard-of-care group. Additional outcomes such as pain scores, OBAS and patient satisfaction scores did not differ between the two groups. Also, perioperative hemodynamics and postoperative outcomes did not differ between the two groups.

The mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI -0.72 – 0.52) and therefore non-inferiority of SST was demonstrated. No previous randomized data were available that report mean postoperative pain scores with SST. An observational study of our first clinical experience with SST did show comparable postoperative pain scores in laparoscopic abdominal and orthopedic surgery.[10] Previous randomized trials with (PC)EA and PCA or iv morphine showed similar pain scores during the first postoperative days.[21-24] This suggests that our results regarding pain scores might be applicable to other settings. It should be noted that this study investigated multimodal treatment strategies, including standard use of paracetamol and if needed metamizole and ketamine besides SST, PCEA or PCA morphine, and therefore no conclusions can be drawn on the effectiveness of the individual components of the treatment strategy. An increase was observed of patients reporting unacceptable pain on postoperative day 3 compared to day 2 in in both groups. This may have been caused by the termination of SST and standard-of-care and (painful) transition to paracetamol and oral or sc opioids.[2] Evidently, more efforts are needed to improve this transition and prevent an upsurge in pain scores when the primary treatment strategy is ended.

The OBAS did not differ significantly between groups. The reported OBAS of the SST group was somewhat higher (a lower score is better) than the standard-of-care group and also higher than reported in a study comparing continuous wound infiltration plus PCA morphine to (PC)EA in patients undergoing open hepato-pancreato-biliary surgery.[24] As we did not separately analyze side effects (mainly nausea, dizziness), we can only hypothesize that OBAS of the SST group was somewhat higher due to more frequently experienced side effects of the SST, and not due to higher pain scores. This possibly also explains why patient satisfaction score were slightly lower in the SST group. A more proactive administration of antiemetics and communication with the patient could be a solution. We did not assess the level of sedation prior to pain scoring or OBAS. Sedation may have affected scores, but it is our experience that residual

sedation is minimal in our patient population following total intravenous anesthesia and preemptive morphine dosing.

Early treatment failure occurred in 24% of patients in the SST group and in 16% of patients in the standard-of-care group (all in the PCEA group; 30%). In a previous randomized trial with SST in open abdominal and orthopedic surgery, the early failure rate was 18%.[12] A disadvantage of SST is that patients need a good cognition, vision and hand-to-mouth coordination in order to operate the system, and careful patient selection (eg low risk for post-operative delirium) is therefore warranted. A meta-analysis performed by us showed similar data of early treatment failure in patients with EA (29%).[3] We did not formally check the position of the PCEA catheter with eg radiography, as this is not part of our standard clinical practice. Patients were analyzed by intention-to-treat approach to avoid potential bias due to exclusion of patients and resemble standard clinical care as much as possible.

EA has been associated with significant vasoactive medication and fluid administration and even impaired anastomotic healing.[25, 26] Perioperative hemodynamics did not differ between groups in this study, yet the sample size could have been too small to detect relevant and significant differences. This also applies to the other postoperative outcomes. The use of SST has a benefit over PCEA and PCA morphine as no epidural catheter or iv line is needed which can hinder the patient from early ambulation and early urinary catheter removal. Unfortunately, no difference was observed regarding urinary catheter removal in the current study.

Several subgroup analyses were performed to confirm the robustness of the results. In intended open procedures, pain scores on postoperative day 3 were lower in the SST group compared to the standard-of-care (PCEA) group. As already mentioned, this might be the result of the (painful) transition to paracetamol and oral or sc opioids.[2] During the original protocol, pain scores on postoperative day 0 and 1 were higher in the SST group compared to the standard-of-care (PCEA) group. We speculate this may be caused by a short learning curve in the use of SST in clinical practice following pancreatoduodenectomy. The subgroup analysis of >65 years showed similar results between SST and standard-of-care, though we would have expected higher pain scores in the SST group since the SST system is more difficult to operate compared to standard-of-care. A possible explanation may be that also for the standard-of-care group patients require a good understanding of the systems as these are also patient controlled methods. There is no one-size-fits-all type of analgesic treatment strategy and for choosing the most appropriate treatment strategy, in the process of shared decision making, the clinician together with the patients should weigh all relevant factors including patient characteristics and the potential advantages and disadvantages of each

different treatment strategy. Careful patient selection, a multimodal treatment strategy and a dedicated and specialized team, including an Acute Pain Service[19], are pivotal for a successful postoperative pain treatment.

This study has several limitations. First, the sample size was small, although large enough to demonstrate non-inferiority of the primary outcome. Due to the small sample size, it is possible some relevant and significant differences were not found for the secondary outcomes (Type II or β error). Second, postoperative day 0 (day of surgery) was not included in the primary outcome since, in our experience, this day is used to establish an adequate level of pain control as modifications of treatment and repetitive instruction of the patient are often needed.[2] Another reason was that the antinociceptive treatment during surgery may have differed among patients with differences in their residual analgesic effects in the first postoperative hours. To investigate possible variations in pain scores during each postoperative day which were not reflected within the mean pain score, we also analyzed proportion of patients that report unacceptable pain and observed no significant difference. Third, the open-label design (no blinding) introduces a the risk of performance bias. Blinding was not done since the treatment strategies were evidently different and blinding of study participants and investigators is not pragmatic and does not resemble standard clinical care. Fourth, two relevant amendments were made to the protocol during the study (allow inclusion of robot-assisted procedures and changing the non-inferiority margin) which might have affected the outcomes. These amendments were reviewed and approved by an independent ethics committee (including a statistical review). Enlarging the inclusion criteria was done as the number of open pancreatoduodenectomies declined rapidly over the last two years in our center, partly related to the COVID-19 pandemic and to the wishes of surgeons and patients to perform a minimal invasive procedure. Minimally invasive pancreatoduodenectomy has been suggested to cause less pain and a faster recovery in non-randomized studies.[27] Stratification for procedure type was used to ensure equal distribution of open and robot-assisted procedures in both groups. The treatment strategies in the standard-of-care group changed due to the inclusion of robot-assisted procedures (from only PCEA to PCEA or PCA morphine). This amendment of the protocol was not in conflict with our goal which was to demonstrate that the SST treatment strategy is a non-inferior alternative to our standard-of-care following pancreatoduodenectomy. The change was regarded as statistically acceptable since our own retrospective data showed that patients with PCEA and PCA morphine following pancreatoduodenectomy reported similar overall mean pain scores on postoperative day 1 to 3 combined. Due to slow accrual, we changed the non-inferiority margin from -1.0 to -1.5 in order to decrease the required sample size. It should be noted that -1.5 is still somewhat strict, as other studies used a margin of -2.0.[21, 28] Multiple subgroup analysis (eg by intended procedure type and protocol version) were performed to check the robustness of the outcomes. And lastly, we

chose not to include secondary outcomes investigating the pharmaco-economics. This should be included in future trials.

In conclusion, this study demonstrated that the SST treatment strategy is a non-inferior analgesic compared to our standard-of-care (PCEA or PCA morphine) in the treatment of pain following pancreatoduodenectomy. In our institution, SST can definitely be added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.

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CHAPTER 15

GENERAL SUMMARY, DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS

In this thesis, several aspects of multidisciplinary management of pancreatic surgery were investigated. This final part summarizes the results and implications of the studies and discusses future perspectives.

General summary and discussion

Part I International evaluation of clinical practice in pancreatic surgery

In **Part I** an overview was provided of clinical practice regarding the use of tumor resection and (neo)adjuvant therapy and outcomes in patients with pancreatic cancer in Europe in a real-world scenario. Also in this part, a survey study among surgeons was performed to obtain a global assessment of perioperative Enhanced Recovery After Surgery (ERAS) practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy.

Chapter 2 describes the use of (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (stage I and II) pancreatic adenocarcinoma in national, regional and a single center cancer registries in the European Registration of Cancer Care (EURECCA) Pancreas Consortium. This study included 3901 patients diagnosed in 2012-2013 of which the majority had stage II disease. The use of neoadjuvant therapy was limited in most registries (3-16%). Large variations in the use of adjuvant therapy (41-70%), 90-day mortality (1-14%) and overall survival exist. Some variation may be explained by the inherent differences between national, regional, and single-center registries. Though, the variations illustrate the difficulty of the implementation of universally accepted guidelines and that results from clinical trials are not easily extrapolated to the general population.

Chapter 3 provides real-world evidence on treatment and survival of elderly patients (≥70 years) with resectable pancreatic cancer stage I-II. The study included 3624 patients diagnosed in 2012-2016 of which the majority had stage II disease. Variations were observed in tumor resection rate (36-50%), rate of (neo)adjuvant chemotherapy (14-56%) and palliative chemotherapy (6-40%). Also differences in outcome were observed regarding 90-day mortality (5-12%), overall survival in patients who underwent tumor resection (median 16-25 months) and overall survival in patients who did not undergo tumor resection (median 4-7 months). The absence of a clear pattern between (neo)adjuvant and palliative chemotherapy and overall survival suggests that further research is needed on selection criteria for (non)-surgical treatment, so that clinicians can tailor treatment and improve overall survival. Although the quantity and quality of randomized clinical trials in pancreatic cancer is increasing, it is still expected that elderly patients will often be excluded from these trials.[1] Therefore, the utilization of cancer registry data offers a solution in research of elderly patients. Another advantage over randomized clinical trial data, is that cancer registry data

is readily available and population-based, thereby minimizing selection bias. EURECCA aims to create awareness of the large variation in treatment strategies between cancer registries, generate new hypotheses for future research and also underlines the need for uniform registration as international comparisons will become increasingly important pillars of international guidelines.[2,3]

Chapter 4 gives insight into the current global perioperative ERAS practices regarding pain management, fluid therapy and thromboprophylaxis in patients undergoing pancreatoduodenectomy. The results of this international survey among 236 surgeons showed that only 61% of pancreatic surgeons practice ERAS protocols and large variations in practices were observed. The preferred method for analgesia was epidural analgesia (50%, EA), followed by intravenous morphine (25%). Restrictive fluid therapy is practiced by 58% of surgeons. Mechanical and chemical thromboprophylaxis are frequently used after pancreatoduodenectomy (90% and 88%), however the duration of chemical prophylaxis varied considerably. In case of minimally invasive surgery, most surgeons only changed the analgesia technique (51%), but did not amend fluid therapy (30%) or thromboprophylaxis (7%). The results of this study will help to create more uniformity of ERAS protocols over the globe and to further optimize the perioperative care after pancreatoduodenectomy by the design of new studies. Also, the observed variations have to be considered during interpretation and extrapolation of study results from another hospital or region.

Part II Surgical and oncological aspects of venous resections in pancreatic surgery

Part II focused on the surgical and oncological aspects of venous involvement in pancreatic surgery. Guidelines are lacking for surgical decision making, postoperative management and pathological grossing techniques of pancreatoduodenectomy with venous involvement (more specific: the portal-superior mesenteric vein [PV-SMV]).

In **Chapter 5**, a systematic literature search was performed to identify international expert surgeons and pathologists who published relevant studies in the last decade. These experts (N=190) and Dutch pancreatic surgeons and pathologists (N=37) were approached to complete an online survey. Several important findings were noted. Correspondence between preoperative imaging, intraoperative findings and pathology regarding venous involvement was considered to be suboptimal. Type 3 reconstruction (segmental resection with primary anastomosis) was most popular (61%). Half of the surgeons expected a higher risk of complications after venous resection, especially PV-SMV thrombosis. Heparinization during venous resection, standard postoperative imaging protocols and thromboprophylaxis regimens differed substantially. Analyzing international expert surgeons compared to Dutch surgeons, the estimated percentage of venous resection was higher, Type 3 venous resection was relatively more often

preferred over Type 1, an increase of the risk of complications after venous resection was less often expected (namely less PV-SMV thrombosis within 90 days after surgery) and they performed the venous resection more often themselves. Most pathologists assess tumor infiltration in the wall of the resected vein. However, only half of the pathologists assess the resection margins of the resected vein itself. Assessment of depth of tumor infiltration differed between pathologists. This study highlights the lack of evidence and emphasizes the need for research on imaging modalities, surgical techniques, postoperative management and standardization of the pathological assessment.

The effect of the type of venous resection (wedge or segmental) on morbidity and survival is poorly understood in current literature.[4-6] Nationwide studies with recent data that represent current clinical practice are lacking. In the international survey most pancreatic surgeons preferred a venous segment resection over a partial venous wedge resection, because of a lower estimated risk of complications. In **Chapter 6** the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival was evaluated. A nationwide retrospective analysis of 1311 patients who underwent pancreatoduodenectomy was performed within the Dutch Pancreatic Cancer Group (DPCG, 2013-2017). A venous resection was performed in 27% patients (65% wedge resection; 35% segmental resection). Patients with segmental resection had more Clavien-Dindo ≥III complications (adjusted odds ratio [OR] 1.90, 95% confidence interval [CI] 1.22-2.98) and worse survival (adjusted hazard ratio 1.40, 95% CI 1.10-1.78) compared to no venous resection. In patients treated with neoadjuvant therapy, survival was comparable between types of venous resection, although patients with segmental resection had more Clavien-Dindo ≥III complications compared to venous wedge and without venous resection (52% versus 19% versus 21%, respectively). The results of this study mainly implicate that an upfront segment resection is associated with poor morbidity and survival. This finding supports recent guidelines in that neoadjuvant chemotherapy should be considered in borderline resectable disease and suspected venous involvement. Improvements in surgical outcome should focus on identifying optimal reconstruction techniques and perioperative protocols in patients who have suspected venous involvement at preoperative imaging. After the results of this study, we started the development of a hands-on workshop on surgical anatomy and operative techniques during venous resection in patients with pancreatic cancer for Dutch pancreatic surgeons.

In **Chapter 7**, we explored the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands in the same cohort as Chapter 6. The number of venous resection per center during the study period varied from 5-52 patients (10-53%) with an annual median of four venous resections per center. There was no clear relationship between

center pancreatoduodenectomy volume and rate or type of venous resection and between anatomical, biological and conditional patient characteristics, center characteristics and rate or type of venous resections per center. Adjusted for predictive factors (female sex, lower BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging), three centers performed significantly more and three centers performed significantly less venous resections than expected. Patients with venous resection in centers with an above median annual volume of venous resections had less postoperative PV-SMV thrombosis, mortality, and major morbidity and longer overall survival. Further research is needed to define the volume-outcome relationship in pancreatoduodenectomy with venous resection and determine its possible clinical relevance. We believe pancreatoduodenectomy with venous resection is technically challenging for the surgeon and also more challenging for the multidisciplinary team (e.g. perioperative hemodynamic monitoring by the anesthesiologist and intensive care team, postoperative thromboprophylaxis by the vascular medicine specialist). Therefore, multidisciplinary efforts are needed to identify best practices, minimize unwanted practice variation among institutions and improve outcomes of patients with pancreatic cancer and suspected venous involvement.

As previously mentioned, one of the main challenges for a pancreatic surgeon when confronted with possible tumor invasion in the PV-SMV is distinguishing tumor from peritumoral inflammation and fibrosis. **Chapter 8** studied the association between venous resection, tumor invasion in the resected PV-SMV, recurrence patterns and overall survival. A multicenter retrospective study of 531 patients who underwent pancreatoduodenectomy for pancreatic cancer (2010-2017) was performed (28% with venous resection). Tumor invasion in the resected PV-SMV was observed in 53% of patients. Patients with venous resection had a higher rate of R1 margin as compared to patients without venous resection (69% versus 37%). Most frequent R1 margins were the PV-SMV (24%) and the superior mesenteric artery margin (20%). Moreover, a very small number of patients had a R1 margin solely at the PV-SMV margin (5%). Venous resection and tumor invasion in the resected PV-SMV were not independent predictors for time to recurrence and overall survival. Additionally, a systematic literature search of large studies (≥500 patients) showed that pathological assessment of the resected PV-SMV is not adequately standardized and studies regarding venous resection and recurrence patterns are scarce. The results of this study have a number of implications. There is need for improvement in patient selection for venous resection, as half of patients do not have tumor invasion in the resected PV-SMV. The promising results of intraoperative ultrasound have led to the initiation of the ULTRAPANC study within the DPCG investigating the added value of intraoperative ultrasound in the assessment of vascular involvement in pancreatic cancer. The high percentage of R1 resections also support recent guidelines in that neoadjuvant chemotherapy should be considered in

(borderline) resectable disease. The fact that only few patients had a R1 margin solely at the PV-SMV margin indicates that a more extensive resection at this margin is often not sufficient to improve radicality. In these patients, neoadjuvant therapy in combination with a TRIANGLE operation and in selected cases also arterial divestment could be considered.[7, 8] Furthermore, the pathological assessment of the resected PV-SMV has now been standardized in the Netherlands.

Part III Surgical complications in pancreatic surgery

Part III consisted of studies on the two most notorious complications in pancreatic surgery: postoperative pancreatic fistula and abdominal infectious complications.

In **Chapter 9** we evaluated surgical strategies (i.e. completion pancreatectomy versus pancreas-preserving procedure) in 162 patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy in nine Dutch institutions (2005-2018). Completion pancreatectomy was associated with higher mortality rate (56 versus 32%; adjusted OR 2.44, 95% CI 1.02-5.85). The meta-analysis of 33 observational cohort studies, including 745 patients, confirmed this finding (random-effects model, OR 1.97, 95% CI 1.03-3.80). In the cohort study, there was no difference between the two groups in the proportion of additional reinterventions after relaparotomy (64 versus 67%, P=0.76) or duration of hospital stay. As this evidence is based on observational studies, residual confounding cannot be ruled out. On the other hand, level 1 evidence is hard to get as the included study population is increasingly rare as a minimally invasive step-up approach seems to be the preferred strategy in the management of pancreatic fistula (e.g. primarily percutaneous catheter drainage and, in case of failure of percutaneous catheter drainage, a pancreas-preserving surgical strategy if possible).[9-11]

To further highlight this, we reacted to a recent study in **Chapter 10**. In their study, Garnier et al. concluded that pancreas-preserving surgical interventions are associated with more reoperations and mortality and that simple surgical drainage should not be adopted.[12] In our cohort, patients who underwent simple surgical drainage and other pancreas-preserving surgical interventions did not differ at baseline. Mortality was 29% following simple surgical drainage versus 37% (range 30-44%) for the other subgroups (P=0.79) and additional reinterventions were performed in 65% following simple surgical drainage versus 70% (range 60-83%) for the other subgroups (P=0.60). Therefore, we believe that, after failure of percutaneous drainage, simple surgical drainage is a viable option in the management of pancreatic fistula following pancreatoduodenectomy

No consensus exists on the predictive role of bile cultures in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy. **Chapter 11** investigated the association between positive bile cultures and abdominal infectious complications after pancreatoduodenectomy in a prospective single center study. We introduced the definition of an isolated organ space infection (OSI): OSI without a simultaneous complication potentially contaminating the intraabdominal space. Intraoperative bile cultures were prospectively and routinely obtained in 114 patients undergoing pancreatoduodenectomy (2016-2019). The positive bile culture rate was 61%, predominantly in patients after preoperative biliary drainage (98% versus 26%). OSIs occurred in 35 patients (31%) and isolated OSIs in nine patients (8%) and were not associated with positive bile cultures (OSIs: OR 0.6, 95% CI 0.25-1.23, isolated OSIs: odds ratio 0.77, 95% CI 0.20-3.04). Complete concordance between microorganisms in the bile and OSI cultures was observed in only one patient. However, our patients received standard antibiotic prophylaxis for five postoperative days, which is different than most other centers where patients for example only receive preoperative antibiotic prophylaxis and postoperative antibiotics only on indication. This may have influenced the results of this single center cohort study. In the meta-analysis, 15 studies reporting on 2047 patients showed no association between positive bile cultures and abdominal infectious complications (pooled OR 1.3, 95% CI 0.98-1.65). Altogether, this study suggests that routinely obtained bile cultures are an inadequate predictor for the development of abdominal infectious complications after pancreatoduodenectomy as well as its causing pathogens and routine performance should be reconsidered. The concept of isolated OSI in pancreatic surgery can be incorporated in future studies.

Part IV Perioperative anesthesiological management in pancreatic surgery

Part IV discussed perioperative anesthesiological management in pancreatic surgery with special regards to analgesic and fluid therapy as patients undergoing pancreatoduodenectomy may experience severe postoperative pain and considerable fluid shift perioperatively.[13-15]

In **Chapter 12** we assessed our own experience with EA and non-EA in 262 patients undergoing open pancreatectomy (2013-2017). EA was used in 73% of patients and there were several important outcomes of the comparison between EA and non-EA patients: (1) initial analgesia was prematurely converted to another form of analgesia in 33% of EA patients versus 11% of non-EA patients; (2) EA patients had lower mean pain scores and fewer reported unacceptable pain on postoperative days 0–1. However, termination of EA led to higher mean pain scores and more patients reported unacceptable pain on postoperative days 3–4, which led to the need for the liberal administration of supplemental opioids; (3) the EA group received more vasoactive medication perioperatively and also cumulative fluid balances were significantly higher on

postoperative days 1–3; (4) postoperative complications and length of hospital stay were similar between both groups. The results of our study implicate that: (1) An adaptation of protocol is required in order to improve pain scores after termination of EA, either by extending the EA phase or by a supplemental preemptive analgesic treatment (opioid or non-opioid), and (2) We need a better alternative for EA and iv morphine, since EA has a high failure rate (33%) and that the most used alternative (iv morphine) provides less pain control.

The systematic review and meta-analysis of available literature **in Chapter 13** aimed to see if EA has superior clinical outcomes compared to non-EA in patients undergoing pancreatoduodenectomy. Three randomized trials and eight cohort studies (25089 patients) were included. EA provided statistically significant though only marginally lower pain scores on postoperative day 0 to 3 compared with iv morphine patients (mean difference -0.50, 95% CI -0.80 - -0.21). Results of separate postoperative days showed lower pain scores in EA patients namely on postoperative days 1 and 2 compared with iv morphine. Treatment failure of EA occurred in 29% of patients, mainly as a results of hemodynamic instability or inadequate pain control. Furthermore, there could be a benefit of EA over iv morphine regarding complications (OR 0.69, 95% CI 0.061-0.79), length of hospital stay (mean difference -2.7 days, 95% CI -2.8 - -2.6) and mortality (OR 0.69, 95% CI 0.51-0.93). Based on these results, we weakly recommend the use of EA over iv morphine as first choice for reducing early postoperative pain in eligible patients undergoing pancreatoduodenectomy. This systematic review showed there are only a few studies available and therefore further research is needed to identify the optimal analgesic technique(s) after pancreatoduodenectomy.

After we reviewed our own experience and evidence available in literature on analgesic management in patients undergoing pancreatic surgery, we designed a randomized trial "*Postoperative Pain relief following Pancreatoduodenectomy (Triple P): sublingual sufentanil versus standard-of-care*". **Chapter 14** described the results of 36 randomized patients (2018-2021) and found that the mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI -0.72 – 0.52) and therefore non-inferiority of sublingual sufentanil compared to standard-of-care (EA or iv morphine) was demonstrated. Early treatment failure occurred in 24% of patients in the sublingual sufentanil group and in 16% of patients in the standard-of-care group. Additional outcomes such as pain scores, Overall Benefit of Analgesia Score and patient satisfaction scores did not differ between the two groups. Also, perioperative hemodynamics and postoperative outcomes did not differ between the two groups. It should be noted that this study investigated multimodal treatment strategies, including standard use of paracetamol and if needed metamizole and ketamine besides sublingual sufentanil or standard-of-care, and therefore no conclusions can be drawn on the effectiveness of the individual components of the

treatment strategy. In our institution, sublingual sufentanil is now added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.

Future perspectives

The incidence of pancreatic cancer is rising and the predicted pancreatic cancer mortality exceeded the breast cancer mortality in Europe in 2017.[16] The indications for pancreatic surgery in (pre-)malignant and benign disease are broadening and the care for pancreatic patients is becoming increasingly complex with a wide variety of medical disciplines involved. Therefore, future studies and multidisciplinary efforts are needed to improve outcomes for pancreatic patients.

Part I International evaluation of clinical practice in pancreatic surgery

Our studies within the EURECCA Pancreas consortium showed that more work needs to been done to uniform and tailor treatment across countries. Well-designed randomized trials, preferably by including international academic and non-academic, teaching and non-teaching hospitals, with adequate external validity have the potential to improve clinical practice. Examples of such trials are the ESPAC, PRODIGE 24–ACCORD and CCTG PA groups. For the subgroup of patients that are not suitable for inclusion in clinical trials, cancer registry based cohort studies are a valuable alternative to further investigate best practices. These studies can provide valuable evidence for the development of (inter) national guidelines since these results can be directly translated to daily practice. Adequate patient selection, prehabilitation, enhanced recovery protocols, and centralization of pancreatic surgery for (elderly) patients to improve outcomes are interesting topics for upcoming research.[17-21] Others have advocated a multidisciplinary approach to high-risk elderly patients undergoing major surgery[22], and several studies have illuminated the importance of geriatric assessment to improve the outcomes of cancer treatment.[23] A recent study in our cohort of pancreatic cancer patients >70 years undergoing pancreatectomy showed that the Safety Management System (VMS) frailty score, risk assessment tool evaluating four geriatric domains: risk for delirium, undernutrition, physical impairments and fall risk, is an useful tool associated with overall survival and discharge not-to-home. This information may be used in the shared decision-making process and the design of new studies.

A recent meta-analysis showed that ERAS programs in pancreatic surgery are safe and effective, can decrease postoperative complication rates, and can promote recovery for patients.[24] Unfortunately, only retrospective case control studies were included in this

analysis. Additional prospective and randomized studies are needed to confirm these findings. Our survey study showed that 61% of surgeons practice ERAS guidelines. The next step is to further optimize, standardize, and implement ERAS guidelines after pancreatic surgery into daily practice. The development and use of an internationally accepted ERAS guideline is pivotal for performing multicenter studies (e.g. allow benchmarking), the subsequent external validity of these results and implementation into clinical practice.

Part II Surgical and oncological aspects of venous resections in pancreatic surgery

The studies on venous resection in pancreatic surgery demonstrated that there is much to gain with regards to patient selection, surgical technique, postoperative management, pathological assessment and follow-up. This will become even more relevant with the increasing use of neoadjuvant therapy in pancreatic cancer.[25, 26] A standardized approach for patients with pancreatic cancer and suspected venous involvement is needed to uniform treatment and could improve outcomes. The upcoming results of our ULTRAPANC study within the DPCG will provide useful data on the assessment of vascular involvement with intraoperative ultrasound. These results will lay the basis for the ULTRAPANC-II study which will focus on the use of intraoperative ultrasound for patient selection for venous resection after neoadjuvant therapy. Furthermore, we have set up a hands-on workshop (surgical anatomy and operative techniques during venous resection) for Dutch pancreatic surgeons and the upcoming PREOPANC-4 trial within the DPCG (investigates the implementation of a best-practice algorithm for patients with locally advanced pancreatic cancer) have the potential to further improve surgical technique and management of patients undergoing venous resection in the Netherlands. Recently defined international benchmark outcomes for pancreatoduodenectomy with venous resection are currently used to assess outcomes within the DPCG and identify areas for further improvement on a hospital, regional or national level.[27] Our nationwide study on the impact of type of venous resection during pancreatoduodenectomy showed a significantly higher rate of PV-SMV thrombosis in patients with venous segment resection and vascular complications (PV-SMV thrombosis or hemorrhage) were the indication in 18 out of 23 patients who underwent relaparotomy after segmental resection. However, no data were available on management and outcome of PV-SMV thrombosis and this is therefore investigated in an ongoing study within the DPCG. In future studies on patient selection, surgical technique, postoperative management, pathological assessment and follow-up it is of upmost importance to use internationally accepted definitions and perioperative standards-of-care.

Part III Surgical complications in pancreatic surgery

In our studies on the surgical treatment of postoperative pancreatic fistula, we confirmed that a minimally invasive step-up approach should be the preferred strategy in the management of pancreatic fistula (e.g., primarily percutaneous catheter drainage

and, in case of failure of percutaneous catheter drainage, a pancreas-preserving surgical strategy if possible). The DPCG recently published the results of the nationwide PORSCH trial which showed that the implementation of a standardized best practice algorithm for early recognition and adequate drainage of postoperative pancreatic fistula after pancreatic resection improves clinical outcomes. This included an approximate 50% reduction in mortality at 90 days.[28] A recent paper on postoperative pancreatic fistula from international pancreatic experts highlighted the importance of dedicated (interventional) radiology and endoscopy and critical care support to avoid unnecessary laparotomies.[29] These experts also advocated for more focus on international top-quality surgical education by for instance sharing and reviewing video content, more randomized clinical trials and more research from a basic science and translational point-of-view on prevention and treatment of postoperative pancreatic fistula.

The study on the bile cultures and abdominal infectious complications resulted in a more critical note about the predictive role of routinely obtained bile cultures. Since expanding antibiotic resistance and stewardship is a relevant topic at this moment, our current postoperative prophylactic antibiotic treatment is being evaluated in a dual center retrospective study (standard antibiotic prophylaxis for five postoperative days versus preoperative antibiotic prophylaxis and postoperative antibiotics on indication). The result of this study may lead to evading unnecessary use of antibiotic prophylaxis. The proportion of patients undergoing preoperative biliary drainage (i.e. bile contamination) is expected to rise due to the increasing use of neoadjuvant chemotherapy in pancreatic cancer.[20, 21] These patients may require an different, or tailor-made, approach. Currently there are several trials ongoing which investigate the optimal preoperative antibiotic prophylaxis, whereas other trials investigate the use of standard versus targeted preoperative antibiotic prophylaxis.[30, 31] The external validity of these trials should be thoroughly scrutinized before implementation into clinical practice, since previous studies have suggested that there is significant interinstitutional variability in bile cultures and antibiotic resistance patterns.[32]

Part IV Perioperative anesthesiological management in pancreatic surgery

In the last part of this thesis, we showed that EA is the most used type of analgesia in patients undergoing pancreatoduodenectomy.[33] Although EA has some marginal advantages over the used alternatives, it cannot unambiguously be recommended for all patients as it has a relatively high failure rate (~30%). The same holds true for sublingual sufentanil. Our randomized trial in a small cohort of patients proved that it can be added to the standard pallet of postoperative analgesia as it was non-inferior to our standard-of-care in the treatment of pain on postoperative day 1 to 3. The increase of pain scores on postoperative day 3 in both groups might be explained by ending the primary pain treatment. In our opinion, more multimodal efforts are needed to improve the transition

from primary to secondary pain treatment and prevent an increase in pain scores. The authors of the recent randomized PAKMAN trial found comparable effectiveness and safety of EA and iv morphine after pancreatoduodenectomy.[34] They also stated that the recommendation for EA in the ERAS guidelines needs critical reconsideration. This is in line with a previous systematic review and meta-analysis of analgesia after abdominal surgery in an ERAS setting could not prove that EA is associated with a shorter duration of hospital stay.[35] More research is needed to determine the optimal analgesic techniques for open and separately for minimally invasive pancreatic surgery. Careful patient selection, a multimodal treatment strategy and a dedicated and specialized team, including the Acute Pain Service[36], are pivotal for a successful postoperative pain treatment.

Conclusions

In this thesis, several aspects to improve the multidisciplinary management of pancreatic surgery were identified, implemented and used to design future studies. More than 15 medical disciplines were involved during the studies involved in this thesis. Highly needed further improvement of outcome of pancreatic patients can be made by multidisciplinary collaborations on a hospital, regional, national and international level.

Table 1. Summary of main findings and answers to the research questions

Chapter 1	**General introduction and outline of this thesis**
PART I	**INTERNATIONAL EVALUATION OF CLINICAL PRACTICE IN PANCREATIC SURGERY**
Chapter 2	**Is there variation in the use of (neo)adjuvant therapies and outcomes of patients who underwent tumor resection for resectable (TNM stage I and II) pancreatic adenocarcinoma in the EURECCA Pancreas Consortium?** The use of neoadjuvant therapy was limited in most registries. Large variations in the use of adjuvant therapy, 90-day mortality and overall survival exists. The differences observed give us the chance to further investigate the best practices and improve outcomes.
Chapter 3	**How are treatment strategies and survival outcomes of patients aged ≥70 years with stage I–II pancreatic cancer in a real-world scenario in the Belgian, Dutch, and Norwegian national cancer registries?** Variations were observed for the rate of tumor resection rate, (neo)adjuvant chemotherapy and palliative chemotherapy. Also differences were observed regarding 90-day mortality, overall survival in patients who underwent tumor resection who did not undergo tumor resection. Future studies should focus on selection criteria for (non)surgical treatment in older patients so that clinicians can tailor treatment.
Chapter 4	**Is there international variation regarding pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy between pancreatic surgeons?** The results of this international survey showed that only 61% of surgeons practice ERAS protocols. Although the majority of surgeons presume a relationship between pain management, fluid therapy and thromboprophylaxis and clinical outcomes, variations in practices were observed. Additional studies are needed to further optimize, standardize and implement ERAS protocols after pancreatic surgery.
PART II	**SURGICAL AND ONCOLOGICAL ASPECTS OF VENOUS RESECTIONS IN PANCREATIC SURGERY**
Chapter 5	**Is there variation regarding surgical management and pathological assessment of pancreatoduodenectomy with suspected venous involvement between international experts and Dutch surgeons and pathologists?** This international survey showed variation in the surgical management and pathological assessment of pancreatoduodenectomy with venous and highlights the lack of evidence and emphasizes the need for research on imaging modalities for improved patient selection, surgical techniques, postoperative management and standardization of the pathological assessment.
Chapter 6	**What is the impact of type of venous resection during pancreatoduodenectomy for pancreatic cancer on postoperative morbidity, mortality and overall survival?** Patients who underwent venous segment resection, and not venous wedge resection, showed more major morbidity and worse overall survival. In the patients who received neoadjuvant therapy, overall survival was markedly higher and showed no difference between the categories of venous resection, whereas major morbidity and postoperative mortality rates remained high after venous segment resection. The results of this study urge the need to improve outcomes in patients who require a venous segment resection.
Chapter 7	**What are the potential causes and the consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands?** Practice variation between institutions in the Netherlands with regards to venous resection and reconstruction during pancreatoduodenectomy for pancreatic cancer were not explained by variations in patient characteristics only. The decision to perform a venous resection is apparently also dependent on variables not available in the registry, and might be associated with characteristics and preferences of the surgical team. The clinical outcomes of venous resection appear to be related to the volume of the procedure.

Chapter 8	**Are venous resection, tumor invasion in the resected vein, recurrence patterns and overall survival associated?** Venous resection and tumor invasion in the resected vein are not associated with recurrence patterns and overall survival. The pathological assessment of the resected portal-superior mesenteric vein has now been standardized in the Netherlands.
PART III	**SURGICAL COMPLICATIONS IN PANCREATIC SURGERY**
Chapter 9	**What should be the preferred surgical strategy when performing a relaparotomy for pancreatic fistula after pancreatoduodenectomy?** Completion pancreatectomy is associated with a doubling of the mortality and a similar rate of additional reinterventions compared to a pancreas-preserving procedure. Based on the current data, a pancreas-preserving procedure seems preferable to completion pancreatectomy in whom relaparotomy is deemed necessary for pancreatic fistula after pancreatoduodenectomy.
Chapter 10	**Correspondence to Garnier et al. and their study on standardized technique for completion pancreatectomy in patients with pancreatic fistula after pancreatoduodenectomy** Simple surgical drainage was not associated with more reinterventions or mortality in our cohort compared to other pancreas-preserving surgical interventions. Therefore, we believe that, after failure of percutaneous drainage, simple surgical drainage is a viable option in the management of pancreatic fistula following pancreatoduodenectomy.
Chapter 11	**Do bile cultures obtained during pancreatoduodenectomy have added value in the prevention or treatment of abdominal infectious complications after pancreatoduodenectomy?** Similar rates of postoperative abdominal infectious complications were observed in patients with positive and negative bile cultures. Regarding the low pathogenicity of the cultured microorganisms and the substantial incidence of confounding non-infectious complications, the predictive value of bile cultures in infectious complications seems limited. Thus, the routine performance of bile cultures should be reconsidered.
PART IV	**PERIOPERATIVE ANESTHESIOLOGICAL MANAGEMENT IN PANCREATIC SURGERY**
Chapter 12	**What are the analgesic and clinical outcomes after epidural and non-epidural analgesia after open pancreatectomy?** In our cohort, patients with epidural analgesia experienced significantly lower pain scores in the first postoperative days compared with non-epidural analgesia, yet higher pain scores after epidural analgesia had been terminated. Although epidural analgesia patients required more vasoactive medication and fluid therapy, the complication rate was similar. We need a better alternative for EA and iv morphine, since EA has a high failure rate and that the most used alternative (iv morphine) provides less pain control.
Chapter 13	**Does epidural analgesia have superior clinical outcomes compared with non-epidural analgesia in patients undergoing pancreatoduodenectomy in current the literature?** Epidural analgesia provides marginally lower pain scores in the first postoperative days than intravenous morphine, and appears to be associated with fewer complications, shorter duration of hospital stay and less mortality. There are only a few studies available and therefore further research is needed to identify the optimal analgesic technique(s) after pancreatoduodenectomy.
Chapter 14	**Is sublingual sufentanil a non-inferior analgesic compared to standard-of-care in the treatment of postoperative pain in patients following pancreatoduodenectomy?** This study demonstrated that the sublingual sufentanil treatment strategy is a non-inferior analgesic compared to our standard-of-care in the treatment of pain following pancreatoduodenectomy. In our institution, sublingual sufentanil can definitely be added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.
Chapter 15	General summary, discussion, future perspectives and conclusions

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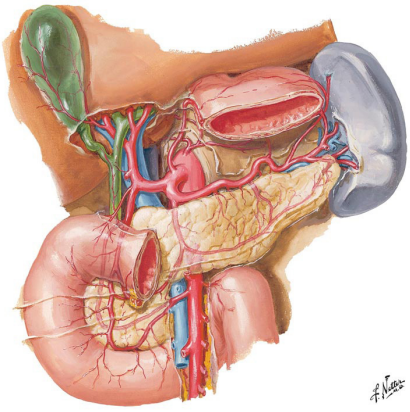
APPENDICES

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 bevat een uitgebreide inleiding en beschrijving van de opbouw van dit proefschrift. Het pancreas (alvleesklier) is een abdominaal retroperitoneaal orgaan van ± 15 centimeter lang met een zalmachtige kleur. Het pancreas is verdeeld in de kop, het lichaam en de staart en heeft een endocriene (bloedsuikerhuishouding) en exocriene functie (spijsverteringssappen). (Pre)maligne afwijkingen zijn de vaakst voorkomende indicaties voor chirurgie aan het pancreas. De pancreatoduodenectomie (Whipple operatie) is de meest uitgevoerde operatie. Bij deze operatie worden de pancreaskop, twaalfvingerige darm en een deel van de galwegen verwijderd en wordt er een reconstructie verricht van het pancreas aan de dunne darm, de maag aan de dunne darm en de galwegen aan de dunne darm. Pancreaschirurgie is complex waardoor ernstige complicaties en zelfs mortaliteit relatief vaak voorkomen. Door verbeteringen van peri-operatieve zorg, chirurgische technieken, en gespecialiseerde centra is de 90 dagen mortaliteit tegenwoordig 2-3%. In Nederland is pancreaschirurgie gecentraliseerd in ziekenhuizen die minstens 20 keer per jaar een pancreatoduodenectomie verrichten.

De prognose van patiënten met een pancreascarcinoom is somber, de mediane overleving van de gehele groep is 4 maanden. De enige behandeling van het pancreascarcinoom met kans op lange termijn overleving bestaat uit chirurgie en peri-operatieve chemotherapie en/of radiotherapie. Helaas komt 80% van de patiënten die gediagnostiseerd wordt met een pancreascarcinoom niet in aanmerking voor chirurgie omdat er reeds sprake is van lokale doorgroei (in grote bloedvaten of omliggende organen) of metastasen. Bij patiënten die wel chirurgie en peri-operatieve chemotherapie en/of radiotherapie ondergaan is de mediane overleving 17-30 maanden.

Bij de zorg voor patiënten die pancreaschirurgie ondergaan zijn veel verschillende chirurgische en niet-chirurgische medische disciplines betrokken; een multidisciplinair team. Het Multidisciplinaire Overleg (MDO) binnen de gezondheidzorg heeft als doel consensus te bereiken over de optimale diagnose, behandeling en follow-up voor een individuele patiënt. Voor patiënten die een operatie ondergaan zijn er specifieke multidisciplinaire richtlijnen, Enhanced Recovery After Surgery (ERAS), met als doel het verminderen van zogenaamde "chirurgische stress" en postoperatieve complicaties.



Dit proefschrift heeft als doel het verbeteren van de multidisciplinaire zorg voor patiënten die pancreaschirurgie ondergaan en is verdeeld in vier onderdelen.

Deel I Internationale evaluatie van klinische praktijk van pancreaschirurgie

Deel I geeft een overzicht van de klinische praktijk en variatie wat betreft tumorresectie en (neo)adjuvante therapie bij patiënten met een pancreascarcinoom in het European Registration of Cancer Care (EURECCA) Pancreas Consortium. Verder zit er in **deel I** een survey-studie uitgevoerd onder chirurgen welke de klinische praktijk van peri-operatieve ERAS elementen pijnbestrijding, vochtbeleid en tromboprofylaxe heeft onderzocht.

Hoofdstuk 2 beschrijft de resultaten van de eerste retrospectieve cohort studie binnen het EURECCA Pancreas Consortium naar het gebruik van (neo)adjuvante chemotherapie bij patiënten die tumorresectie ondergingen van een resectabel (stadium I/II) pancreascarcinoom. Deze studie includeerde 3901 patiënten uit 7 datasets op nationaal-, regionaal- en ziekenhuis-niveau. Variatie werd geobserveerd wat betreft neoadjuvante chemotherapie (3-16%), adjuvante chemotherapie (41-70%), 90 dagen mortaliteit (1-14%) en lange termijn overleving. Een deel van de variatie kan verklaard worden door de inherente verschillen tussen de datasets. De resultaten laten zien dat (internationale) richtlijnen nog onvoldoende geïmplementeerd zijn en dat resultaten van gerandomiseerde studies niet zomaar overeenkomen met de algemene niet-geselecteerde patiëntenpopulatie.

Een recente internationale cohort studie liet zien dat 70 jaar de mediane leeftijd is ten tijde van diagnose van patiënten met een pancreascarcinoom, terwijl de mediane leeftijd in de grote gerandomiseerde studies 61-65 jaar is. Oudere patiënten worden dus vaker geëxcludeerd in belangrijke klinische gerandomiseerde studies. In **Hoofdstuk 3** werd dit kennistekort onderzocht in een retrospectief cohort van patiënten ≥70 jaar met een resectabel pancreascarcinoom (stadium I/II). Deze studie includeerde 3624 patiënten uit 3 nationale datasets. Variatie werd geobserveerd wat betreft tumor resectie (36-50%), (neo)adjuvante chemotherapie (14-56%), palliatieve chemotherapie (6-40%), 90 dagen mortaliteit (5-12%), overleving na tumor resectie (mediaan 16-25 maanden) en overleving zonder tumorresectie (mediaan 4-7 maanden). Er werd geen duidelijk verband gevonden tussen het gebruik van (neo)adjuvante chemotherapie, palliatieve chemotherapie en overleving. Dit suggereert dat meer onderzoek nodig is naar de juiste selectiecriteria voor de juiste behandeling. Door middel van goed opgezette gerandomiseerde studies, bij voorkeur internationale multicenter studies met verschillende soorten ziekenhuizen, kunnen de uitkomsten van patiënten met een pancreascarcinoom verbeterd worden. Voor patiënten die niet geïncludeerd kunnen worden in dit soort studies biedt onderzoek met (kanker)registratie datasets een oplossing. Dit soort datasets hebben de bijkomende voordelen dat ze vaak makkelijk beschikbaar zijn en weinig selectie bias bevatten.

Hoofdstuk 4 beschrijft de resultaten van de survey-studie onder 236 chirurgen welke de klinische praktijk van peri-operatieve ERAS elementen pijnbestrijding, vochtbeleid en tromboprofylaxe heeft onderzocht. De ERAS richtlijn werd gebruikt door 61% van de chirurgen en binnen de verschillende elementen was veel variatie. De meest gebruikte pijnbestrijding was epidurale pijnstilling (50%) gevolgd door intraveneus morfine (25%). Een restrictief vochtbeleid werd gebruikt door 58% van de chirurgen. Mechanische (90%) en medicamenteuze (88%) tromboprofylaxe werd veel gebruikt na pancreatoduodenectomie, echter werd er veel variatie geobserveerde betreft de duur, dosering en type tromboprofylaxe. Deze studie laat zien dat er meer werk verricht moet worden om de ERAS richtlijn wereldwijd te implementeren. Recente studies, retrospectieve cohort studies en meta-analyses hiervan, hebben laten zien dat ERAS richtlijnen de uitkomsten kunnen verbeteren van patiënten die pancreaschirurgie ondergaan. Prospectieve gerandomiseerde studies moeten deze resultaten bevestigen, zodat de implementatie en ontwikkeling bespoedigd kan worden. Verschillen in klinische praktijk zouden in overweging genomen moeten worden bij het interpreteren van resultaten van onderzoeken uit een ander land, regio of ziekenhuis.

Deel II Chirurgische en oncologische aspecten van veneuze resecties tijdens pancreaschirurgie

Deel II van dit proefschrift zijn de chirurgische en oncologische aspecten van veneuze resecties (vena porta/vena mesenterica superior) tijdens pancreaschirurgie onderzocht. Door de groeiende indicaties voor neoadjuvante therapie bij patiënten met een pancreascarcinoom worden veneuze betrokkenheid en veneuze resecties een steeds belangrijker onderwerp binnen de pancreaschirurgie.

In **Hoofdstuk 5** werden internationale experts (N=190) en Nederlandse (N=37) chirurgen en pathologen ondervraagd over het onderwerp veneuze betrokkenheid/resecties (survey studie). De overeenkomst tussen pre-preoperatieve beeldvorming, intra-operatieve beoordeling en pathologische bevindingen betreft veneuze betrokkenheid wordt suboptimaal bevonden. Internationale expert chirurgen prefereren duidelijk een Type 3 veneuze resectie (segment resectie, 65%), terwijl Nederlandse chirurgen zowel Type 3 als Type 1 (wedge resectie, 45 en 40%) prefereren. Veel variatie werd geobserveerd in type en duur van tromboprofylaxe na een veneuze resectie, terwijl een trombose van de vena porta/vena mesenterica superior de meest gerelateerde complicatie is. De pathologische beoordeling van de veneuze resectie is niet gestandaardiseerd, alhoewel bijna alle pathologen tumor invasie van de vene beoordelen (93%). Deze survey studie laat zien dat er meer onderzoek en standaardisatie nodig is voor patiënten met veneuze betrokkenheid: met name voor patiëntselectie, chirurgische technieken, postoperatieve protocollen en pathologische beoordeling.

Hoofdstuk 6 is een retrospectieve cohort studie in alle 18 ziekenhuizen in Nederland die pancreaschirurgie deden en onderzocht de invloed van type veneuze resectie op korte en lange termijn resultaten. Deze studie includeerde 1311 pancreascarcinoom patiënten die een pancreatoduodenectomie ondergingen, waarvan 27% met veneuze resectie (35% segment, 65% wedge). Patiënten die een veneuze segment resectie ondergingen hadden significant meer postoperatieve tromboses (18 versus 5 versus 1%) en ernstige complicaties (39 versus 20 *versus* 23%) en een kortere overleving (mediaan 12 versus 16 versus 20 maanden) vergeleken met patiënten die een wegge of geen veneuze resectie ondergingen. Na neoadjuvante therapie hadden deze patiënten een gelijke overleving, terwijl het percentage ernstige complicaties hoog was (52 versus 19 versus 21%). Deze studie bevestigd dat neoadjuvante therapie overwogen moet worden voor patiënten met veneuze betrokkenheid. De korte en lange termijn resultaten van een veneuze segment resectie waren slechter vergeleken met de literatuur. Om de uitkomsten voor deze patiënten te verbeteren hebben we een "hands-on" veneuze resectie cursus (mei 2022) georganiseerd voor Nederlandse chirurgen onder begeleiding van internationale experts.

In Hoofstuk 6 werd variatie geobserveerd in het verrichten van een veneuze resectie tussen de verschillende ziekenhuizen in Nederland (10-53%). **Hoofdstuk 7** onderzocht in ditzelfde retrospectieve cohort de mogelijke oorzaken en gevolgen van deze praktijkvariatie om uiteindelijk tot betere standaardisatie en uitkomsten te komen. In deze studie werd geen verband gevonden tussen het percentage of aantal veneuze resectie dat een ziekenhuis uitvoert en patiënt karakteristieken of ziekenhuis volume. Persoonlijke ervaring en voorkeur van het chirurgisch team spelen mogelijk een belangrijke rol (aangepaste odds ratio tussen ziekenhuizen 0.15-2.33). In de ziekenhuizen die jaarlijks >4 veneuze resectie verrichten werden minder postoperatieve complicaties (22 versus 38%) en mortaliteit (2 versus 11%) en langere overleving (mediaan 16 versus 12 maanden) geobserveerd. Verder onderzoek is nodig om de klinische relevantie van deze volume-uitkomst relatie te bevestigen. Naar onze mening is veneuze resectie tijdens pancreaschirurgie niet alleen een technische uitdaging voor de chirurg maar ook een uitdaging voor het multidisciplinaire team (hemodynamiek door anesthesiologie en intensive care, tromboseprofylaxe door de vasculair geneeskundige, pathologische beoordeling etc.).

Als het gaat om veneuze betrokkenheid is het per-operatief onderscheiden van daadwerkelijke tumor invasie en peri-tumorale ontsteking lastig voor een chirurg. Dit is een klinisch relevant vraagstuk, omdat het gaat om het wel of niet verrichten van een veneuze resectie. In **Hoofstuk 8** werd de associatie tussen veneuze resectie, tumor invasie, recidief patronen en overleving onderzocht. In deze multicenter retrospectieve cohort studie werken 531 pancreascarcinoom patiënten geïncludeerd die pancreatoduodenectomie ondergingen in 3 ziekenhuizen. Van de 28% patiënten

die een veneuze resectie ondergingen had 53% daadwerkelijk tumor invasie in de gereseceerde vene. Patiënten die een veneuze resectie ondergingen hadden vaker een irradicale resectie (69 versus 37%). De meeste patiënten hadden een irradicale veneuze resectie marge, echter in maar 5% van de patiënten was dit de enige irradicale resectie marge. Veneuze resectie en tumor invasie in de vene waren geen prognostische factoren voor recidieven of overleving. Deze studie laat zien dat er betere selectiecriteria nodig zijn voor het verrichten van een veneuze resectie. De lopende ULTRAPANC studie is een prospectieve studie in 3 ziekenhuizen naar intra-operatieve echografie van vaatbetrokkenheid bij patiënten met een pancreascarcinoom, de resultaten zullen binnenkort verschijnen. Inmiddels is er ook een internationale ULTRAPANC II studie onderweg welke meer specifiek de waarde van intra-operatieve echografie onderzoekt in patiënten met veneuze betrokkenheid die neoadjuvant zijn behandeld zijn. Verder ondersteunen de studies in dit proefschrift dat neoadjuvante therapie overwogen dient te worden bij patiënten met veneuze betrokkenheid. Uitgebreide chirurgie alleen zal waarschijnlijk niet leiden tot meer radicale resecties. Mogelijk dat intensieve neoadjuvante therapie, samen met een resectie zoals de TRIANGLE operatie of "arterial divestement", kan leiden tot betere uitkomsten. De aanstaande PREOPANC-4 studie gaat een best-practice algoritme introduceren in Nederland voor de patiënten met een lokaal irresectabel pancreascarcinoom (met name veroorzaakt door arteriële betrokkenheid) en zal hopelijk ook leiden tot betere uitkomsten. De pathologische beoordeling van een preparaat met veneuze resectie is nu gestandaardiseerd in Nederland. Dit maakt toekomstige vergelijkingen en onderzoek naar de prognostische waarde mogelijk.

Deel III Chirurgische complicaties na pancreaschirurgie

Deel III van dit proefschrift gaat over gevreesde complicaties na pancreaschirurgie: postoperatieve pancreasfistels en abdominale infectieuze complicaties. Bij een postoperatieve pancreas fistel lekt er pancreassap met eroderende enzymen in de vrije buikholte wat leidt tot ontsteking, infectie, necrose en bloedingen. Abdominale infectieuze complicaties is een verzamelnaam voor bijv. abcessen en peritonitis.

Er is beperkt bewijs voor de juiste behandeling van postoperatieve pancreasfistels waarbij de patiënt dermate klinisch achteruitgaat dat een chirurgische interventie verricht dient te worden. In **Hoofdstuk 9** werd een multicenter retrospectief cohort onderzoek gecombineerd met een systematische review en meta-analyse van beschikbare literatuur waarbij de uitkomsten van een complementerende pancreatectomie versus pancreas-sparende operatie werden geëvalueerd. In de cohort studie werden 162 patiënten geïncludeerd uit 9 ziekenhuizen. Patiënten die een complementerende pancreatectomie (N=26) ondergingen hadden een significant hogere mortaliteit (56 versus 32%; aangepaste odds ratio 2.44, 95% CI 1.02-5.85). Dit werd bevestigd in de systematische review en meta-analyse van 33 studies met 745 patiënten. Deze studie

suggereert dus dat een pancreas-sparende operatie geprefereerd dient te worden. **Hoofdstuk 10** geeft een reactie op een recente Franse studie die concludeerde dat een pancreas-sparende operatie met alleen chirurgische drainage niet verricht dient te worden in deze patiëntengroep. Een subgroep analyse, van hetzelfde cohort gebruikt in Hoofstuk 9, laat zien dat chirurgische drainage in deze studie niet leidt tot mindere uitkomsten. De analyses in hoofdstuk 9 en 10 ondersteunen de heersende consensus van de minimaal invasieve "step-up-approach" welke overgekomen is uit de behandeling van patiënten met een acute necrotiserende pancreatitis. De recent gepubliceerde PORSCH studie binnen de DPCG liet zien dat een algoritme voor het tijdig herkennen en behandelingen van complicaties na pancreaschirurgie kan leiden tot een verder afname van de mortaliteit.

De galweganastomose is de meest voorkomende oorzaak van abdominale infectieuze complicaties wanneer deze niet veroorzaakt worden door postoperatieve pancreasfistels. Er is geen consensus over de rol van intra-operatieve galkweken in het voorspellen en behandelen van abdominale infectieuze complicaties. In **Hoofdstuk 11** werd de associatie tussen gecontamineerde galwegen en abdominale infectieuze complicaties na pancreatoduodenectomie onderzocht in een prospectief cohort en opnieuw een systematische review en meta-analyse. In deze studie werden 114 patiënten geïncludeerd die een pancreatoduodenectomie ondergingen waarvan 61% een positieve intra-operatieve galkweek had (98% versus 28% bij wel/niet pre-operatieve galwegdrainage). Positieve intra-operatieve galkweken waren niet geassocieerd met abdominale infectieuze complicaties en geïsoleerde abdominale infectieuze complicaties (geen postoperatief pancreasfistel of galweganastomose lekkage). Dit werd bevestigd door de meta-analyse van 15 studies en 2047 patiënten. De resultaten van het retrospectief cohort zijn moeilijk in perspectief te plaatsen, omdat de geïncludeerde patiënten 5 dagen lang post-operatief antibiotica kregen, wat uitzonderlijk is in de huidige literatuur. Het juist gebruik van antibiotica en de groeiende resistentie patronen is op dit moment hot-topic, daarom worden momenteel verschillende studies opgezet naar de rol van galwegcontaminatie en antibioticagebruik binnen de pancreaschirurgie.

Deel IV Perioperatieve anesthesiologie van pancreaschirurgie

Deel IV van dit proefschrift gaat over de peri-operatieve anesthesiologische aspecten van pancreaschirurgie met speciale aandacht voor pijnbestrijding en vochtbeleid. Patiënten die een pancreatoduodenectomie ondergaan kunnen heftige postoperatieve pijn en grote vochtvolume veranderingen ervaren.

Hoofdstuk 12 beschrijft de resultaten van een retrospectief cohort onderzoek van 262 patiënten die een pancreasresectie ondergaan. In deze studie werden patiënten met (73%) en zonder (27%) epidurale pijnstilling vergeleken (89% van deze patiënten kreeg

intraveneus morfine). Bij 1 op de 3 patiënten met epidurale pijnstilling werd deze vroegtijdig beëindigd, met name door hemodynamische instabiliteit of onvoldoende pijnstilling (33 versus 11%). Patiënten met epidurale pijnstilling hadden significant lagere pijnscores op dag 0 en 1, echter het stoppen van epidurale pijnstilling op dag 3 leidden tot een toename van pijnscores. De cumulatieve vochtbalans op dag 1, 2 en 3 was significant hoger in patiënten met epidurale pijnstilling, terwijl postoperatieve complicaties en opnameduur gelijk waren aan de patiënten zonder epidurale pijnstilling. Deze studie laat zien dat het kans op falen van epidurale pijnstilling hoog is en dat de beschikbare alternatieven minder goede pijnstilling geven.

In **Hoofdstuk 13** werd een systematische review en meta-analyse verricht om te kijken of epidurale pijnstilling leidt tot betere uitkomsten in patiënten die een pancreatoduodenectomie ondergaan. Drie gerandomiseerde studies en 8 cohort studies werden geïncludeerd met 25089 patiënten. Epidurale pijnstilling gaf marginaal betere pijnstilling op dag 0 t/m 3 vergeleken met intraveneus morfine (verschil in pijnscore -0.50, 95% CI -0.80 - -0.21). Dit effect kwam vooral door dag 1 en 2. Epidurale pijnstilling werd in 29% van de patiënten vroegtijdig gestopt. Patiënten met epidurale pijnstilling hadden minder complicaties (met name pneumonie) en een kortere opnameduur. Alhoewel de kracht van het bewijs matig is, lijkt er een voordeel te zijn voor patiënten met epidurale pijnstilling.

De retrospectieve cohort studie, de systematische review en meta-analyse en recente goede ervaringen met sublinguaal sufentanil (niet invasief, snelle werking, en weinig bijwerkingen) leidden tot gerandomiseerde studie die beschreven staan in **Hoofdstuk 14.** In deze gerandomiseerde studie werden 36 patiënten die een pancreatoduodenectomie ondergingen gerandomiseerd voor "standard-of-care" (epidurale pijnstilling of intraveneus morfine) of sublinguaal sufentanil. Patiënten met sublinguaal sufentanil hadden geen hogere pijnscores dan patiënten met "standard-of-care" (-0.10, 95% CI -0.72 – 0.52). Vroegtijdig stoppen van behandeling werd gezien in 24% van de patiënten met sublinguaal sufentanil (misselijkheid en niet kunnen bedienen van het apparaat) versus 16% van de patiënten met "standard-of-care". Overige klinische uitkomsten waren niet verschillend tussen beide groepen. Sublinguaal sufentanil kan nu met goede onderbouwing worden toegevoegd aan het palet van pijnstilling na pancreatoduodenectomie. Verder onderzoek is nodig om te kijken of deze resultaten ook haalbaar zijn in andere ziekenhuizen. Juiste patiëntselectie, multimodale behandeling en een Acute Pijn Service team zijn essentieel voor een succesvolle pijnbestrijding na pancreaschirurgie.

Hoofdstuk 15 bevat een uitgebreide samenvatting en discussie van de studies in dit proefschrift. Rondom dit proefschrift zijn meerdere soorten studies verricht, met meer dan 15 verschillende betrokken medische disciplines. Samenvattend zijn in dit proefschrift

verschillende aspecten geïdentificeerd en geïmplementeerd om de multidisciplinaire zorg voor patienten die pancreaschirurgie ondergaan te verbeteren en gebruikt om verder onderzoek op te zetten. Toekomstig onderzoek om de uitkomsten van patienten die pancreaschirurgie ondergaan te verbeteren dient multidisciplinair van aard te zijn en op ziekenhuis, regionaal, nationaal en internationaal niveau verricht te worden.

CURRICULUM VITAE

Jesse Vincent Groen was born in The Hague in The Netherlands on July 9th 1991. During high school in Deventer he was actively involved in the student parliament, working as a tutor for student in chemistry, physics, biology, mathematics and economics and he played football at the Koninklijke Utile Dulci. He started medical school at the Leiden University Medical Center (LUMC) in 2009.

During medical school, he participated in several committees at the university and the student society of Minerva. In 2011 he started working at BISLIFE, where he learned how to retrieve postmortem ocular, cardiovascular and musculoskeletal tissues for transplantation. This is when he became enthusiastic about surgery. During the surgical internship he met Dr. Sven Mieog and started to build a prospective pancreatic surgery database of the LUMC. This turned out to be the start of the PhD project that resulted in this thesis. His research allowed him to collaborate with 14 medical disciplines involved with pancreatic surgery. He tutored 10 research students and scientific internships. From 2018-2020 he was the Secretary of the multidisciplinary South West Pancreatic Cancer Care working group.

After three years of research he started working at the Department of Surgery at the Alrijne Hospital in 2020. In 2021, he started his surgical training at the Department of Surgery at the Alrijne Hospital. Jesse currently lives in Amsterdam.

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Book chapter publication

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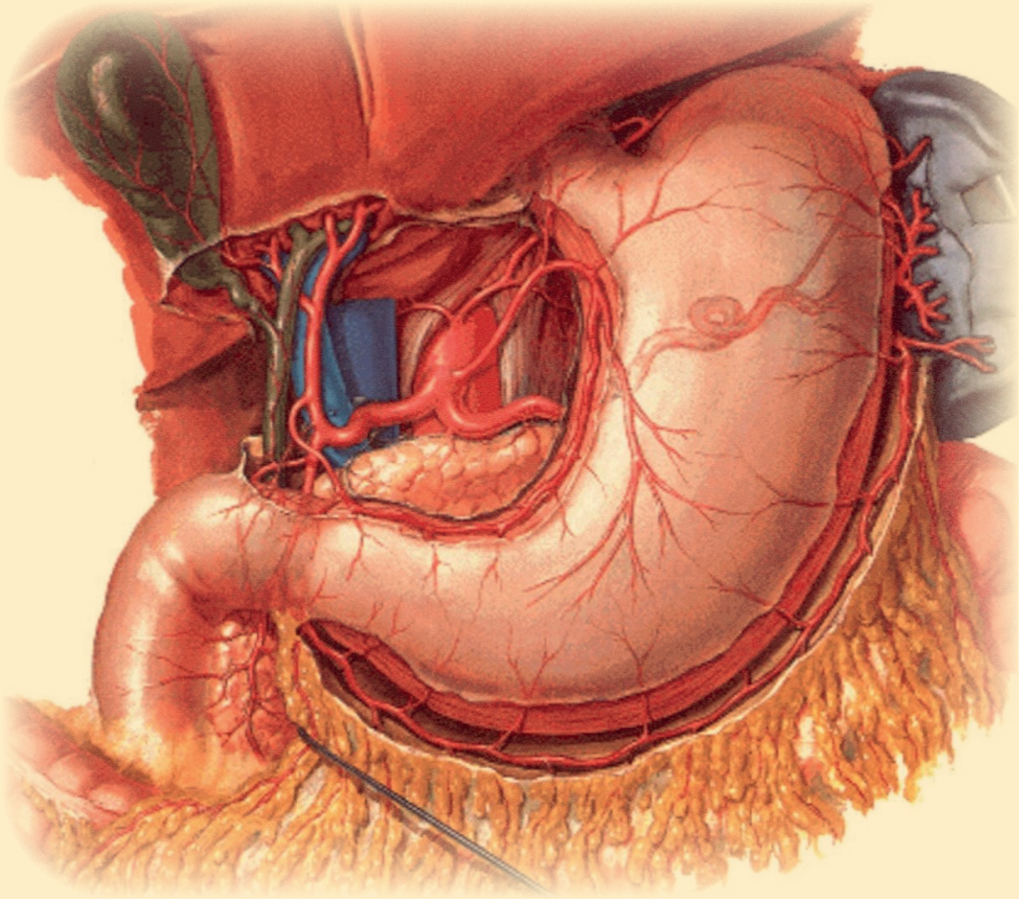

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