Improving outcomes of pancreatic surgery

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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

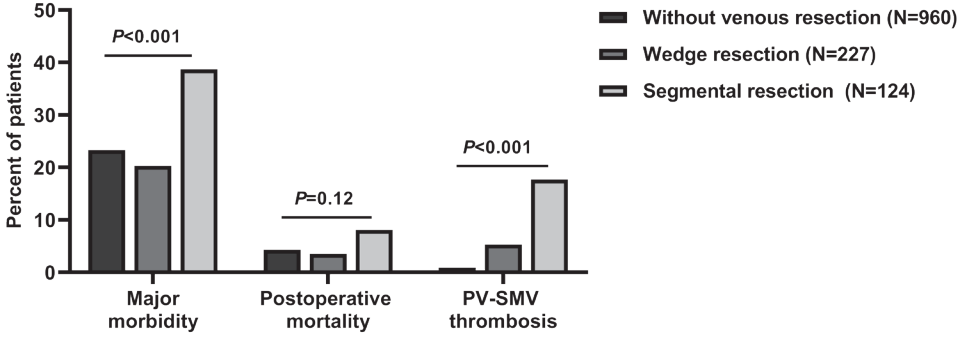


Figure 1. Major morbidity (Clavien-Dindo grade ≥III), postoperative mortality and portal vein-superior mesenteric vein thrombosis after pancreatoduodenectomy for pancreatic cancer by category of venous resection

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

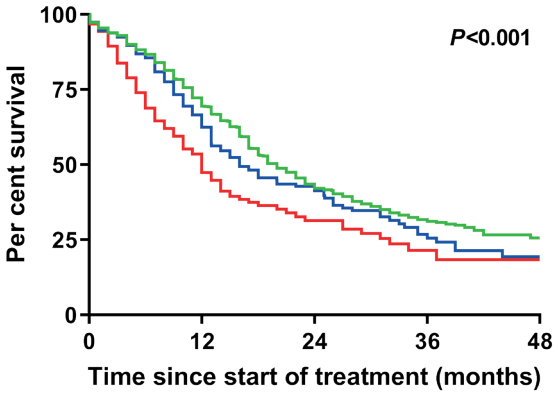
pN-stage[i]	**N1**	-	-	-	1.11	0.92-1.36	0.29
	N2	-	-	-	1.45	1.17-1.80	0.001
pM-stage[j]	**M1**	-	-	-	1.22	0.79-1.89	0.36
Tumour differentiation grade[k]	**Moderate**	-	-	-	1.55	1.17-2.04	0.002
	Poor/Undifferentiated	-	-	-	2.26	1.69-3.02	<0.001
Lymphangio invasion[a]		-	-	-	1.10	0.92-1.31	0.30
Perineural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

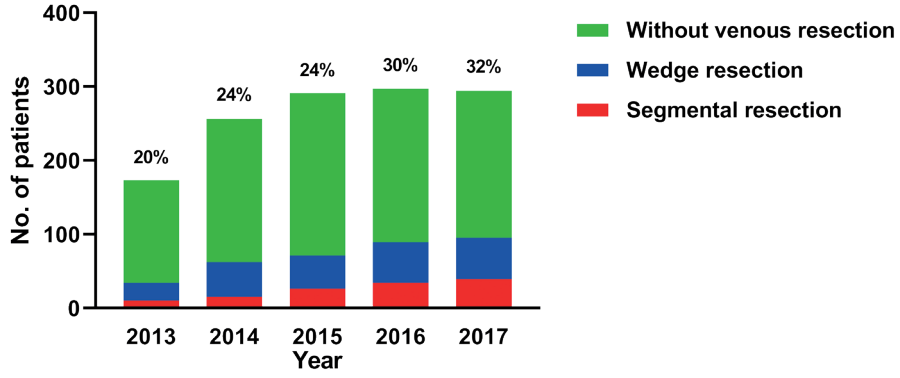


Figure S1. Pancreatoduodenectomies performed with and without venous resection over the study period

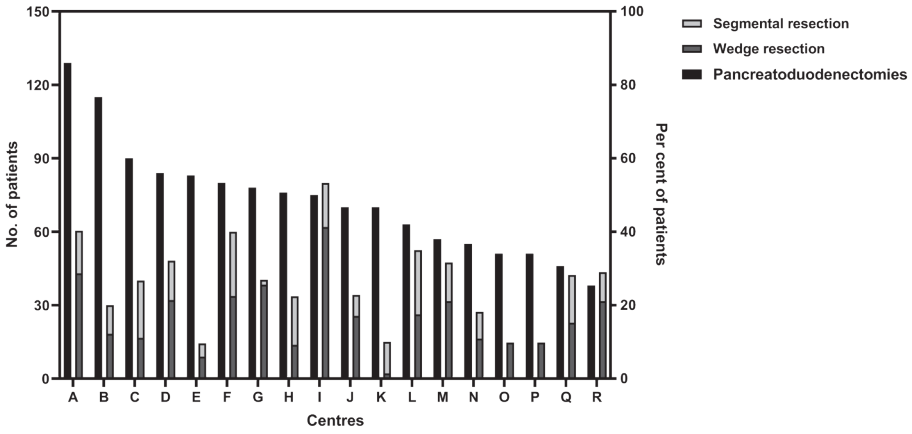
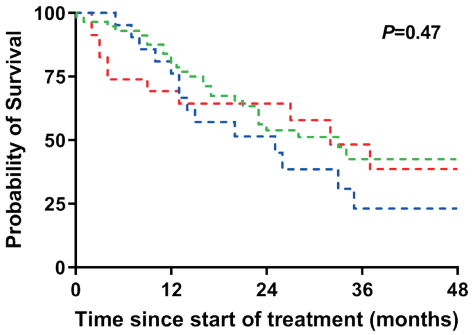


Figure S2. No. of pancreatoduodenectomies (plotted at left y-axis) and per cent of venous wedge and segment resection (plotted at right y-axis) for pancreatic cancer per centre performed over the study period



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

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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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