Improving outcomes of pancreatic surgery

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CHAPTER 7

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

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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).

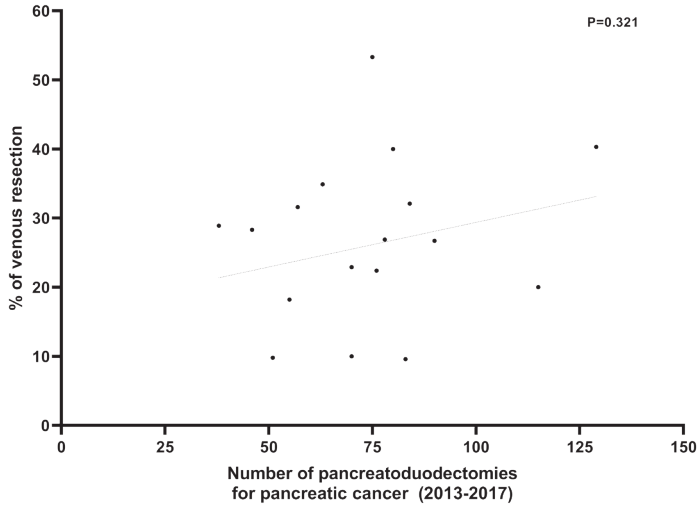

Figure 1. Relationship between center volume and rate of venous resections

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

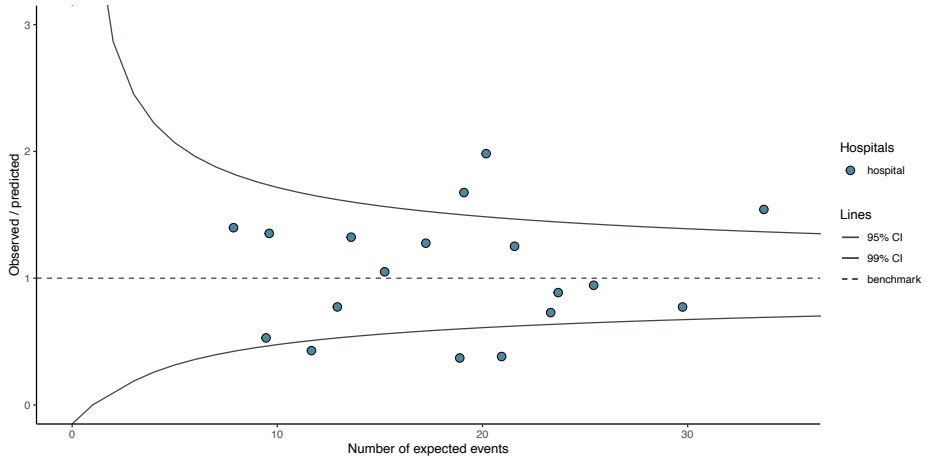

Figure 2. Funnel plot of adjusted center practice variation in the use of venous resection during pancreatoduodenectomy for pancreatic cancer (adjusted for sex, BMI, neoadjuvant therapy, venous involvement and venous stenosis on imaging)

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).

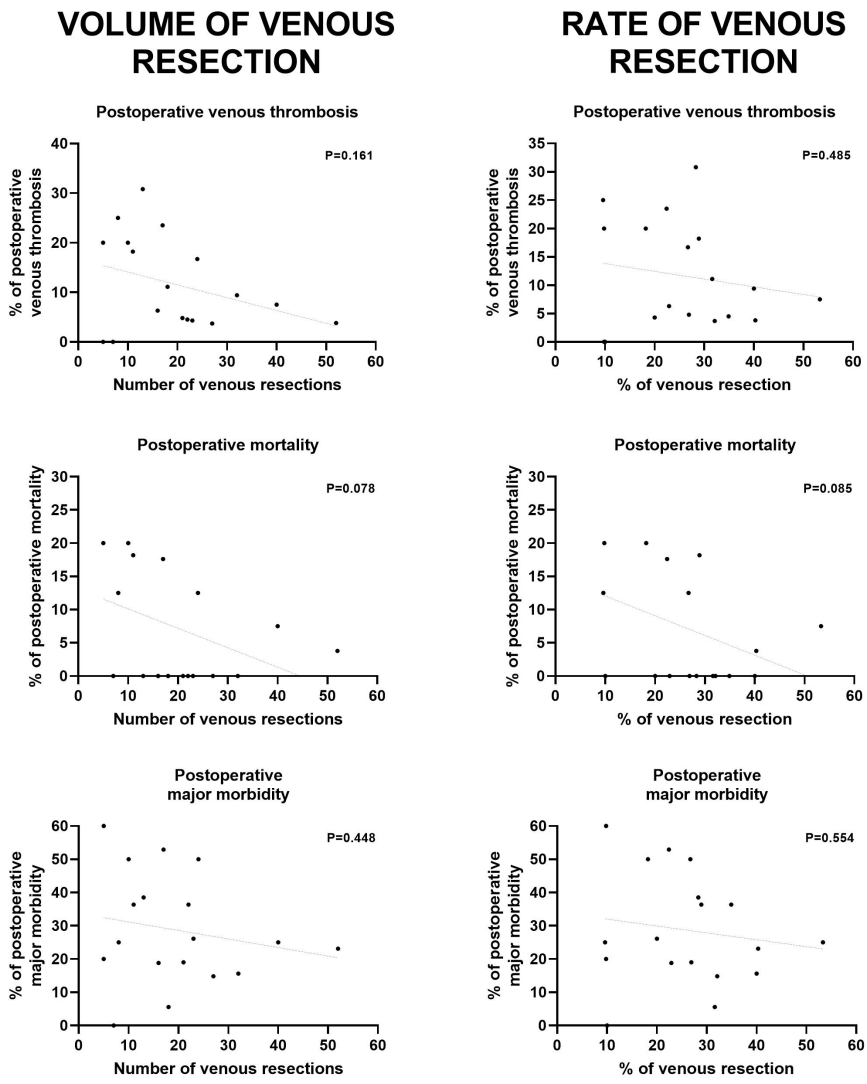

Figure 3. Relationship between volume (left column) and rate (right column) of venous resections and postoperative outcomes

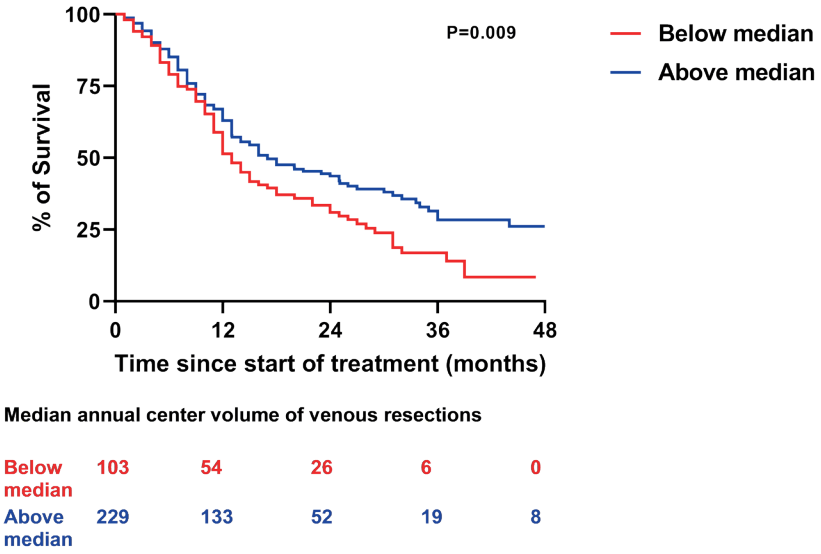

Figure 4. Kaplan–Meier curves of overall survival after start of treatment (day of surgery or start of neoadjuvant therapy) for pancreatic cancer stratified for median annual center volume of venous resections (below: ≤4; above: >4 venous resections)

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

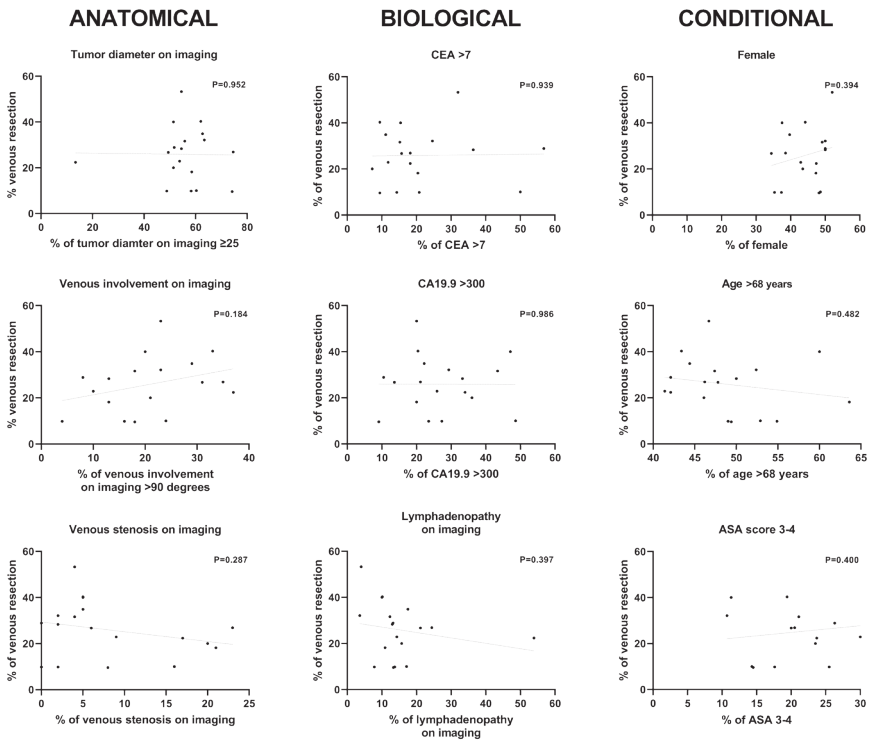

Figure S1. Relationship between rate of venous resections and anatomical, biological and conditional patient characteristics

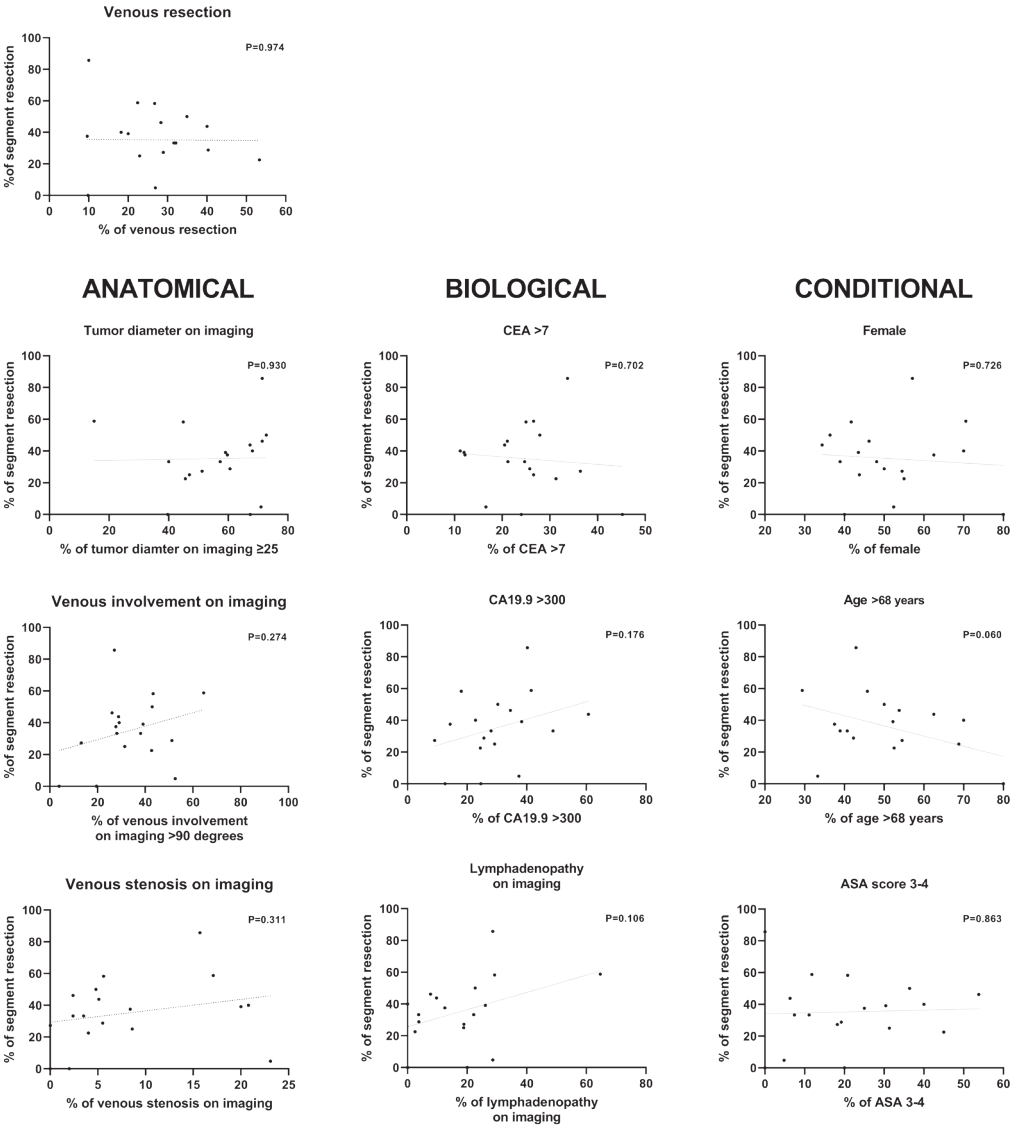

Figure S2. Relationship between venous segment resection and rate of venous resections and anatomical, biological and conditional patient characteristics

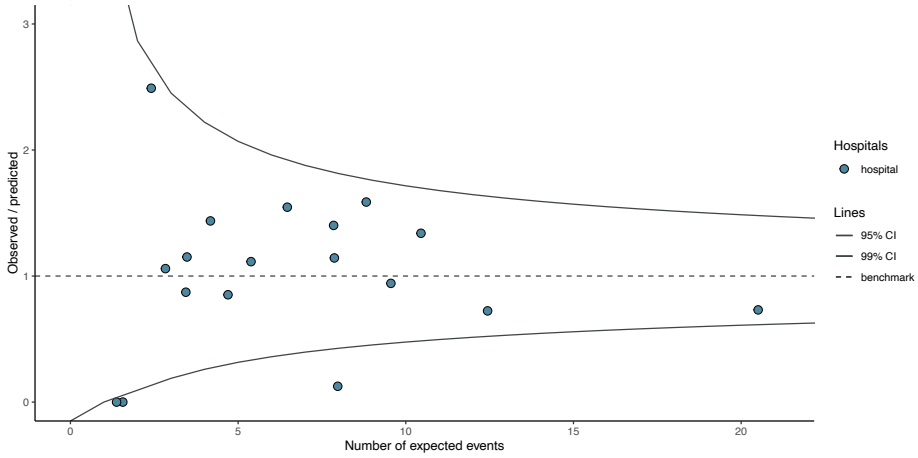

Figure S3. Funnel plot of adjusted center practice variation in the use of venous segment resection during pancreatoduodenectomy for pancreatic cancer (adjusted for neoadjuvant therapy and venous involvement on imaging)

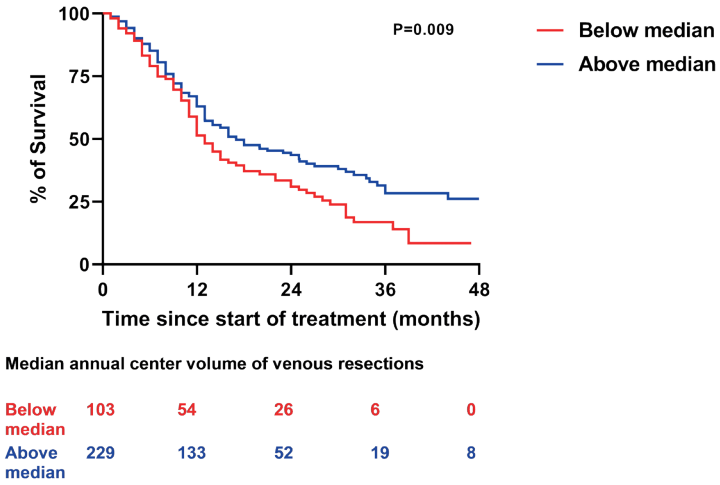

Figure S4. Kaplan–Meier curves of overall survival after start of treatment (day of surgery or start of neoadjuvant therapy) for pancreatic cancer, in patients without postoperative mortality (death within 90 days following surgery), stratified for median annual center volume of venous resections (below: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