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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 1,311 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 the 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 body mass index, neoadjuvant therapy, venous involvement, and stenosis on imaging were predictive for

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venous resection. Adjusted for these factors, 3 centers performed significantly more, and 3 centers performed significantly fewer 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) were observed in centers with an above-median annual volume of venous resections (>4).

Conclusion: Patient and tumor characteristics did not explain significant practice variation between centers in the Netherlands in venous resection during pancreatoduodenectomy for pancreatic cancer. 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 the 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, PV-SMV thrombosis, and overall survival of patients undergoing venous segment resection in the Netherlands are worse than 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 into the associated factors concerning surgical procedures and patient and center characteristics. It has been suggested that venous resection during pancreatic surgery should be performed only at high-volume centers with experienced surgical and multidisciplinary teams.[4,11] Volume–outcome relationships in pancreatic surgery in the Netherlands have already been proven and have shown 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 the 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

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 Strengthening the Reporting of Observational Studies in Epidemiology criteria.[17]

Data collection

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

Definitions

Carcinoembryonic antigen and carbohydrate antigen 19-9 were scored as the highest preoperative values, and previously published cutoff values were used for categorization.[18] Resectability criteria were defined according to the DPCG criteria: no arterial involvement and venous involvement $\leq 90^\circ$ was considered resectable; arterial involvement $\leq 90^\circ$ and/or venous involvement 91° to 270° without occlusion was considered borderline resectable, arterial involvement $>90^\circ$ and/or venous involvement $>270^\circ$ 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 the absence of a fat plane between the tumor and PV-SMV and was categorized as $\leq 90^\circ/>90^\circ$. Portal or superior mesenteric vein 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. The type of venous resection was classified according to the International Study Group of Pancreatic Surgery guidelines[4] and reported by a 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 after surgery was scored based on imaging studies performed at the attending physician's discretion. The Clavien–Dindo classification was scored within 30 days after surgery, and grade ≥III was considered to be major morbidity.[21] Postoperative mortality was defined as death within 90 days after surgery unless the cause of death was clearly disease-related (eg, 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 histologic classification.[23] An R1 resection margin was defined as the presence of tumor cells within 1 mm of

Table I
Baseline characteristics of patients stratified for venous resection

Variable	Category	Venous resection				*P* value
		No		Yes		
		N	%	N	%	
Total		960	73.2	351	26.8	-
Preoperative characteristics						
Sex	Male	554	57.7	180	51.3	.038
	Female	406	42.3	171	48.7	
Age (y), median (IQR)		68 (61–74)		68 (61–74)		.747
BMI (kg/m^2), median (IQR)		25.1 (4.2)		24.3 (3.7)		.008
ECOG	0–1	858	89.7	306	87.7	.286
	2–4	98	10.3	43	12.3	
ASA	I–II	742	77.3	273	77.8	.852
	III–IV	218	22.7	78	22.2	
Preoperative weight loss (%), median (IQR)		9 (6–13)		10 (6–14)		.170
CEA (ug/L), median (IQR)		3.4 (2.2–5.8)		4.3 (2.3–5.8)		.099
CA19-9 (ku/L), median (IQR)		94 (21–298)		140 (32–512)		.024
Preoperative biliary drainage		542	56.5	203	57.8	.656
Neoadjuvant therapy		57	5.9	44	12.5	< .001
Neoadjuvant therapy*	Chemo-radiotherapy	33	3.4	25	7.1	> .999
	Chemotherapy	24	2.5	19	5.4	
Tumor diameter on imaging (mm), median (IQR)		25 (19–31)		27 (20–33)		.008
Venous involvement on imaging	≤90	827	86.2	189	53.8	< .001
	>90	133	13.9	162	46.2	
Venous stenosis on imaging		55	5.8	60	18.6	< .001
Lymphadenopathy on imaging		147	15.3	56	16.0	.796
Preoperative resectability status†	Resectable	781	83.4	174	50.4	< .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	.832
	PPPD	591	61.6	213	60.7	
	PRPD	22	2.3	10	2.8	
Minimally invasive procedure		109	11.4	14	4.0	< .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	.057
Additional resection		51	5.3	22	6.3	.504
Duration of surgery (min), median (IQR)		295 (239–377)		360 (290–437)		< .001
Blood loss during surgery (mL), median (IQR)		600 (350–1000)		800 (500–1466)		< .001
Postoperative characteristics						
Postoperative PV-SMV thrombosis		9	0.9	34	9.7	< .001
Postoperative mortality		41	4.3	18	5.1	.507
Postoperative major morbidity		224	23.3	94	26.8	.197
Adjuvant therapy		647	68.2	236	67.7	.830

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA19-9*, carbohydrate antigen 19-9; *CEA*, carcinoembryonic antigen; *ECOG*, Eastern Cooperative Oncology Group; *PPPD*, pylorus preserving pancreatoduodenectomy; *PRPD*, pylorus resecting pancreatoduodenectomy; *PV-SMV*, portal or superior mesenteric vein.
* Patients who received neoadjuvant therapy.
† According to the Dutch Pancreatic Cancer Group criteria.
‡ According to the International Study Group of Pancreatic Surgery criteria.

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, major postoperative 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 versus below median [median >4 vs ≤4]). Sensitivity analysis was performed with other thresholds of venous resections' median annual center volume.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 23.0 (IBM SPSS, Inc, Armonk, NY). 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 IQR and compared using the Kruskal–Wallis test. Categorical variables were presented as frequencies with percentages and compared using the χ^2 analysis or Fisher exact test. Overall survival was reported as the median with a 95% 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

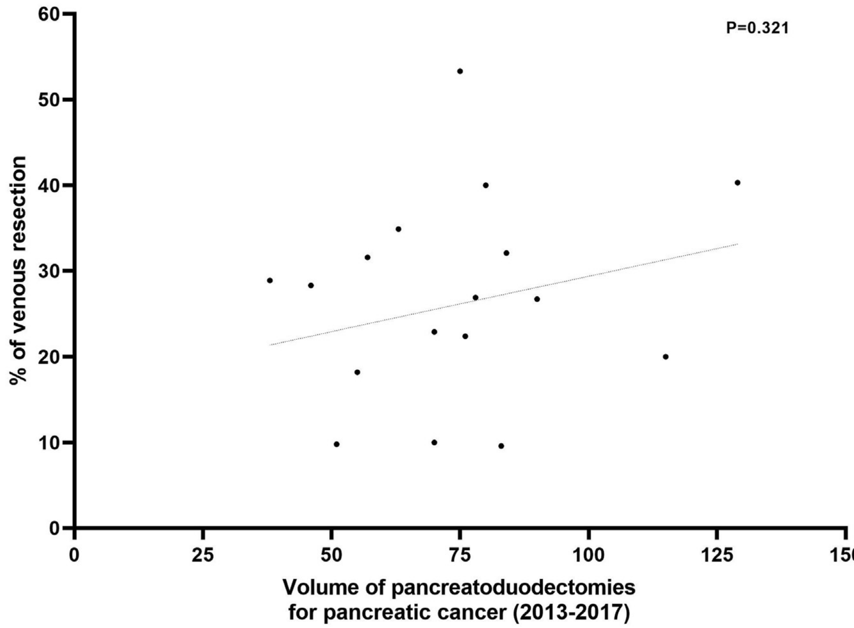


Figure 1. Relationship between center volume and rate of venous resections.

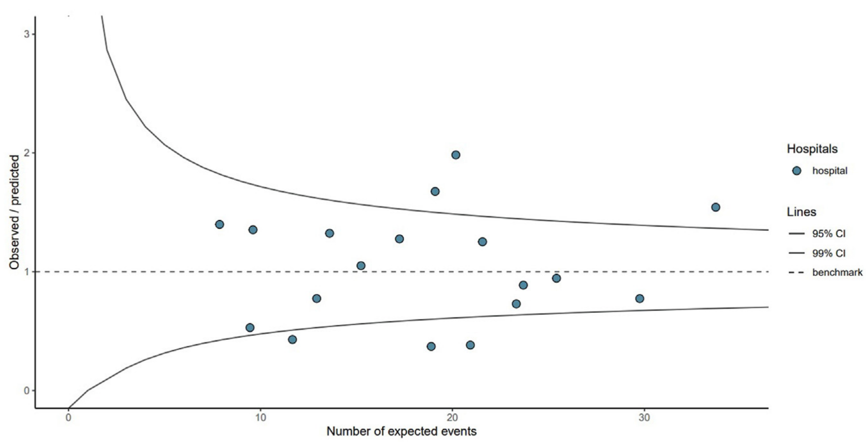


Figure 2. Funnel plot of adjusted center practice variation in the use of venous resection during pancreatoduodenectomy for pancreatic cancer (adjusted for sex, body mass index, neoadjuvant therapy, venous involvement, and venous stenosis on imaging).

using observed/expected ratios adjusted for the identified preoperative predictive factors (analysis in R version 4.1.0 [R Foundation for Statistical Computing, Vienna, Austria]. The observed/expected ratio indicates if a center performed more (>1) or fewer (<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 the 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, 1,311 patients undergoing pancreatoduodenectomy for pancreatic cancer were included, of whom 351 (27%) had a venous resection (Table I). Preoperative and intraoperative characteristics of patients stratified for venous resection are shown in Table I. 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).

Practice variation among centers concerning performing venous resection

There was no relationship between the 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 (carcinoembryonic antigen, carbohydrate antigen 19-9, lymphadenopathy on imaging), and conditional patient characteristics (sex, age, American Society of Anesthesiologists [ASA] score) and the rate of venous resections per center (Supplementary Figure S1).

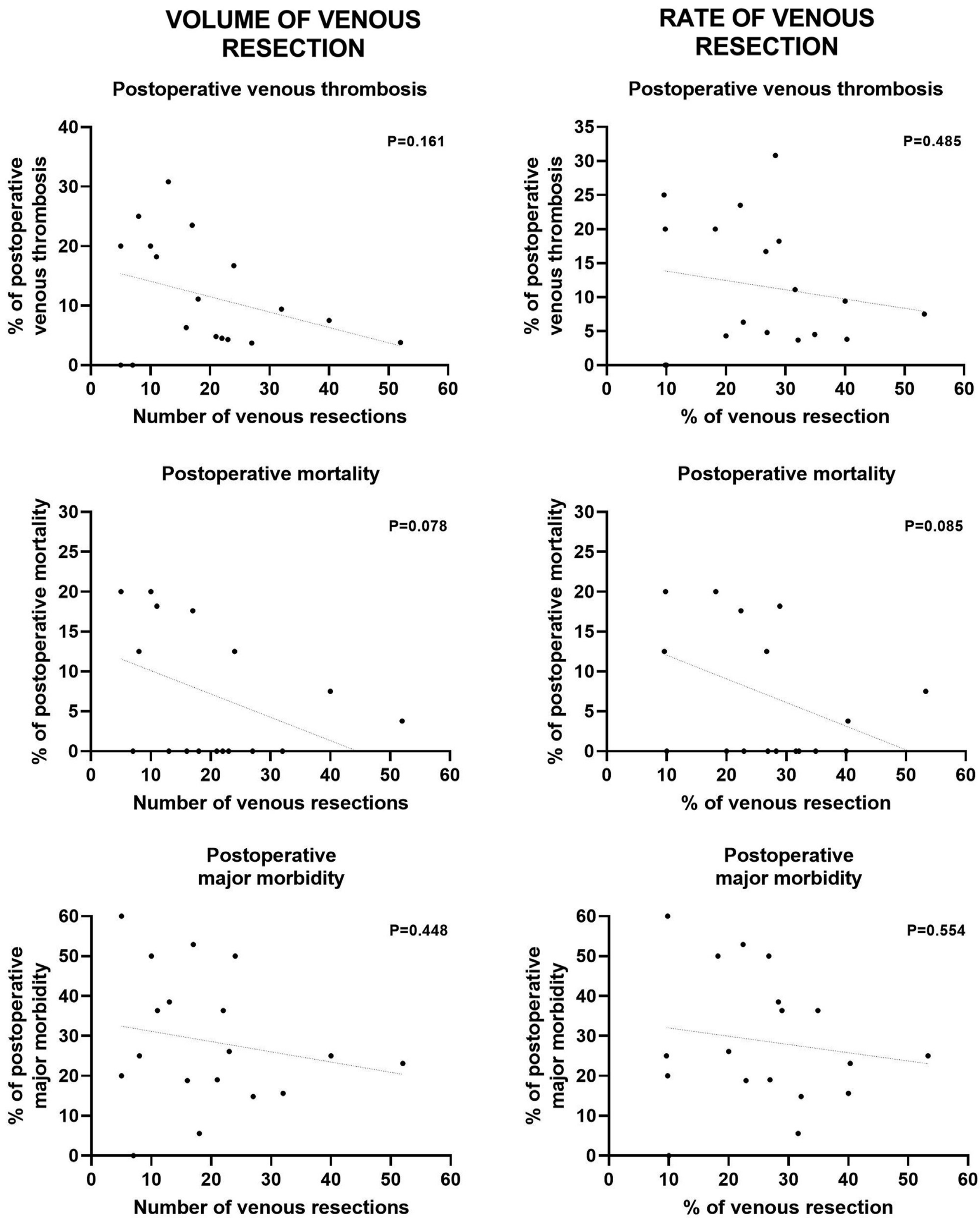


Figure 3. Relationship between volume (left column) and rate (right column) of venous resections and postoperative outcomes.

In univariable analysis, female sex, lower body mass index, neoadjuvant therapy, venous involvement, and venous stenosis on imaging were predictive factors for venous resection. Adjusted for these factors, 3 centers performed significantly more, and 3 centers performed significantly fewer venous resections than predicted (Figure 2).

The rate of venous segment resection (versus wedge resection) varied from 0 to 86% between centers, and there was no

Table II
Baseline, postoperative and histopathologic characteristics of patients with venous resection stratified for median annual center volume of venous resections

Variable	Category	Median annual center volume of venous resections				P value
		Below (≤4)		Above (>4)		
		N	%	N	%	
Total		116	33.0	235	67.0	
Preoperative characteristics						
Sex	Male	53	45.7	127	54.0	.141
	Female	63	54.3	108	46.0	
Age (y), median (IQR)		69 (62–74)		68 (61–73)		.678
BMI (kg/m^2), median (IQR)		24.1 (22.1–26.6)		23.8 (21.7–26.0)		.229
ECOG*	0–1	105	90.5	201	86.3	.255
	2–4	11	9.5	32	13.7	
ASA	I–II	88	75.9	185	78.7	.544
	III–IV	28	24.1	50	21.3	
Preoperative biliary drainage		64	55.2	139	59.1	.478
Neoadjuvant therapy		13	11.2	31	13.2	.597
Preoperative resectability* status	Resectable	60	53.1	114	49.1	.788
	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	.933
	Fibrotic/hard	70	66.7	139	66.2	
Pancreatic duct diameter in mm, median (IQR)		7 (4–10)		6-4-9)		.465
Blood loss during surgery in mL, median (IQR)		1,000 (600–1,750)		700 (450–1,200)		.001
Type of venous resection†	Type 1	58	50.0	139	59.1	.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	.001
Postoperative mortality		13	11.2	5	2.1	< .001
Postoperative major morbidity		44	37.9	50	21.3	.001
Adjuvant therapy		69	60.0	167	71.4	.033
Histopathologic characteristics						
Resection margins status	R0	38	32.8	86	36.6	.479
	R1	78	67.2	149	63.4	
Tumor size on pathology in mm, median (IQR)		32 (25–40)		34 (25–40)		.816
pN stage	N0	29	25.0	64	27.2	.898
	N1	46	39.7	89	37.9	
	N2	41	35.3	82	34.9	
M stage	M0	114	98.3	228	97.0	.484
	M1	2	1.7	7	3.0	
Tumor differentiation grade	Good	9	8.6	27	12.7	.390
	Moderate	57	54.3	119	56.1	
	Poor/undiff.	39	37.1	66	31.1	
Lymphangio invasion		75	72.8	100	56.5	.007
Perineural invasion		92	87.6	187	90.8	.386

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *ECOG*, Eastern Cooperative Oncology Group; *PV-SMV*, portal or superior mesenteric vein.
* According to the Dutch Pancreatic Cancer Group criteria.
† According to the International Study Group of Pancreatic Surgery criteria.

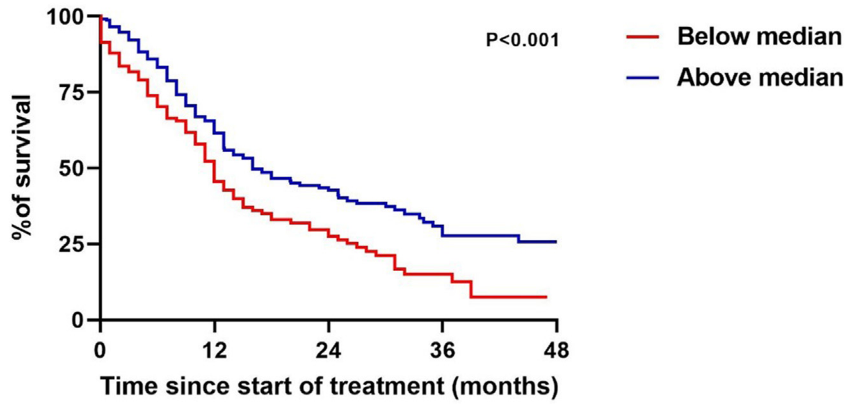
relationship between the rate of venous resections, anatomical, biological, and conditional patient characteristics, and rate of venous segment resection per center (Supplementary Figure S2). In univariable analysis, neoadjuvant therapy and venous involvement in imaging were predictive factors for venous segment resection. Adjusted for these factors, 3 centers performed significantly fewer venous segment resections than expected (Supplementary Figure S3).

Practice variation regarding the volume of venous resection and postoperative outcomes

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

Preoperative, intraoperative, postoperative, and histopathologic characteristics stratified for above (>4) and below (≤4) median annual center volume of venous resections are shown in Table II. Patients with venous resection in centers with an above-median annual volume of venous resections had less blood loss during surgery ($P = .001$), underwent less often a venous segment resection (32% vs 43%, $P = .032$), and less often had lymphangio invasion (57% vs 73%; $P = .007$). Other preoperative, intraoperative, postoperative, and histopathologic (eg, resection margin status) characteristics were not different between above and below the 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%, $P = .001$), mortality (2% vs 11%, $P < .001$), and major morbidity (22% vs 38%, $P = .001$), less often had lymphangio invasion (57% vs 73%, $P = .007$), and had longer overall survival (median 16 vs 12 months, $P < .001$) (Figure 4). An analysis of overall survival in patients without postoperative mortality showed a similar difference (median 17 months vs 13 months, $P = .009$) (Supplementary Figure S4).

In a multivariable analysis for major postoperative morbidity, centers with an above-median annual volume of venous resections (OR = 0.45, 95% CI = 0.24–0.85), venous segment



Median annual center volume of venous resections

	0	12	24	36	48
Below median	116	54	26	6	0
Above median	233	133	52	19	8

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).

resection (OR = 2.28, 95% CI = 1.18–4.41), female sex (OR = 1.90, 95% CI = 1.00–3.61), and ASA score III to IV (OR = 2.40, 95% CI = 1.20–4.80) were predictive factors (Table III). In a multivariable analysis for overall survival, centers with an above-median annual volume of venous resections (hazard ratio [HR] = 0.68, 95% CI = 0.50–0.92), ASA score III to IV (HR = 1.64, 95% CI = 1.16–2.31), and poor/undifferentiated differentiation grade were predictive factors. Multivariable analysis for postoperative PV-SMV thrombosis and mortality was not performed due to the low volume of events (respectively, $N = 34$ and $N = 18$). Sensitivity analysis with a median annual center volume of ≤6 versus >6 and ≤9 versus >9 venous resections are shown in Supplementary Tables S1 to 4. Three centers had a median annual volume of >6 venous resections and were predictive for favorable postoperative major morbidity (OR = 0.46, 95% CI = 0.21–1.00) and overall survival (HR = 0.60, 95% CI = 0.43–0.85) in multivariable analysis. Only 1 center had a median annual volume of >9 venous resections and was not predictive of a difference in major postoperative morbidity and overall survival.

Discussion

This nationwide study of 1,311 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 body mass index, neoadjuvant therapy, venous involvement, and venous stenosis on imaging), 3 centers performed significantly more, and 3 centers performed significantly fewer 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 this variation's potential background and impact. The choice to perform a venous resection and reconstruction type is multifactorial and likely based on the combination of surgical teams' preferences and skills and patient anatomy (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 the 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 the percentage of patients with venous involvement and the percentage of venous resections per center. Little is known about which details motivate the decision, and no standardized guidelines exist on this topic. Awareness of the observed practice variations in this study will lead to efforts to identify best practices, standardizing the approach for patients with pancreatic cancer and suspected venous involvement to improve outcomes.

Several studies have shown an increase in 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 centers 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 has led to the 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,

Table III
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	.014
Type of venous resection	Wedge	Reference			
	Segment	2.278	1.178	4.408	.014
Sex	Male	Reference			
	Female	1.903	1.004	3.608	.049
Age (y)		0.993	0.959	1.028	.681
BMI (kg/m^2)		0.966	0.884	1.055	.440
ASA score	I–II	Reference			
	III–IV	2.399	1.201	4.795	.013
Preoperative biliary drainage	No	Reference			
	Yes	1.337	0.710	2.516	.368
Neoadjuvant therapy	No	Reference			
	Yes	1.633	0.649	4.108	.297
Pancreatic duct diameter (mm)		0.928	0.847	1.016	.106
Texture pancreatic remnant	Normal/soft	Reference			
	Fibrotic/hard	0.935	0.482	1.814	.842
Blood loss during surgery (mL)		1.000	1.000	1.000	.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	.012
Type of venous resection	Wedge	Reference			
	Segment	1.305	0.967	1.761	.081
Sex	Male	Reference			
	Female	1.087	0.801	1.474	.594
Age (y)		1.012	0.996	1.030	.150
BMI (kg/m^2)		0.976	0.934	1.021	.289
ASA score	I–II	Reference			
	III–IV	1.637	1.161	2.310	.005
Neoadjuvant therapy	No	Reference			
	Yes	0.898	0.542	1.486	.675
Resection margin status	R0	Reference			
	R1	1.509	1.085	2.098	.015
Tumor diameter on pathology (mm)		0.990	0.977	1.003	.147
pN stage	N0	Reference			
	N1	0.909	0.625	1.322	.617
	N2	1.255	0.853	1.847	.249
pM stage	M0	Reference			
	M1	0.845	0.256	2.793	.783
Tumor differentiation grade	Good	Reference			
	Moderate	1.451	0.849	2.480	.174
	Poor/undiff.	2.017	1.165	3.492	.012
Lymphangio invasion	No	Reference			
	Yes	0.849	0.614	1.173	.321
Perineural invasion	No	Reference			
	Yes	1.046	0.691	1.582	.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 ($N = 3$), tumor differentiation grade ($N = 34$), lymphangio invasion ($N = 71$), perineural invasion ($N = 40$).
ASA, American Society of Anesthesiologists; *BMI*, body mass index.

no association was found between the 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 the median annual center volume of ≤6 versus >6 venous resections, although not for the higher threshold of ≤9 versus >9. This might be related to case-mix factors and sample size, as only 1 hospital performed a median of >9 annual venous resections during the study period. Further studies are needed to define the volume–outcome relationship in pancreatoduodenectomy with venous resection and to determine its possible clinical relevance.

We believe pancreatoduodenectomy with venous resection is technically challenging for the surgeon and more challenging for the multidisciplinary team (eg, 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 our previous[6] and present study results, 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 led to minimalization of practice variation and standardization of the approach in the Netherlands, ultimately improving outcomes.

This study has limitations. First, the risk of information and classification bias should be considered due to the retrospective design and data collection. 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); therefore, results cannot be directly extrapolated to health care systems with no or other centralization methods. These different health care 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 limited the generalizability of the results (only 8% neoadjuvant therapy versus 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 (eg, selection for neoadjuvant therapy and venous resection) was made in the clinical and surgical context of the patient. The results of the 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, and the cutoff is low and relatively arbitrary (overall median annual center volume of only 4 venous resections); in addition, the retrospective design of the study and, therefore, the results might be susceptible to bias. Furthermore, the cutoff is not externally validated and is 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 the 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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Conflict of interest/Disclosure

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Supplementary materials

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