Improving outcomes of pancreatic surgery

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CHAPTER 8

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

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

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

MATERIALS AND METHODS

Study Design and Patient Selection

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

Data Collection

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

Definitions

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

Outcomes and Comparisons

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

Literature Overview

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

Statistical Analysis

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

RESULTS

Baseline Characteristics

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

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

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

Pathology Characteristics

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

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

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

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

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

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

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

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

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

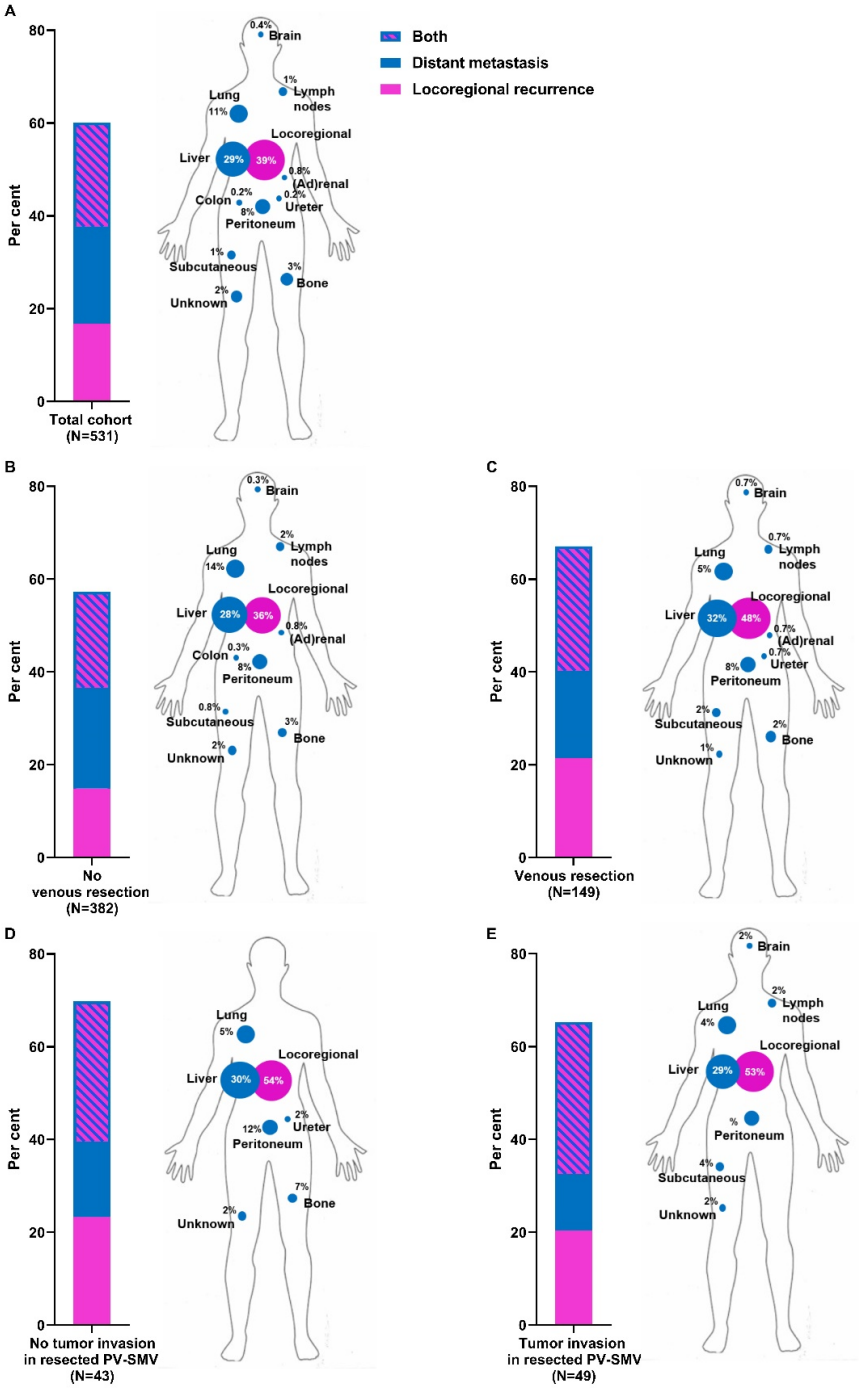

Figure 1A-E. Patterns of recurrence for (A) the total cohort, (B) venous resection, (C) no venous resection, (D) tumor invasion in resected PV-SMV, (E) no tumor invasion in resected PV-SMV.

Recurrence Patterns and Overall Survival

Recurrence Patterns

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

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

Overall Survival

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

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

Literature Overview

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

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

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

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

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

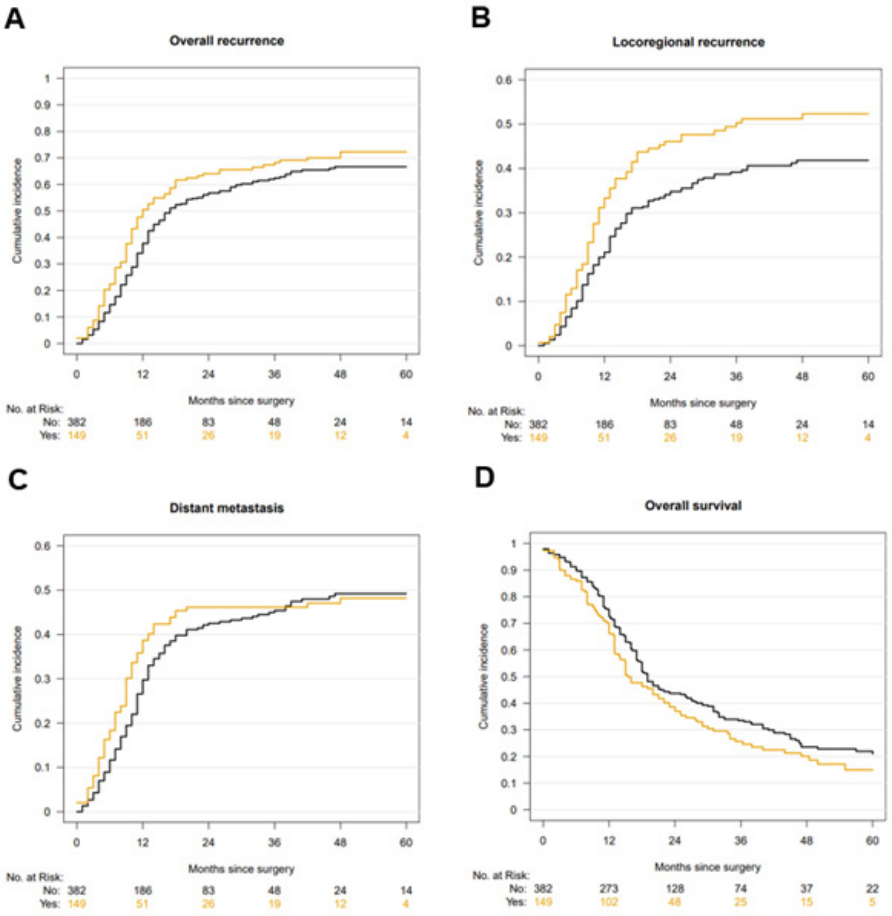

Figure 2A-D. Cumulative incidence curves by venous resection (No/Yes) for (A) overall recurrence (Gray's test: P=0.039), (B) locoregional recurrence (Gray's test: P=0.013), (C) distant metastasis (Gray's test: P=0.46). (D) Kaplan-Meier curve of overall survival by venous resection (No/Yes)(log-rank test: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

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

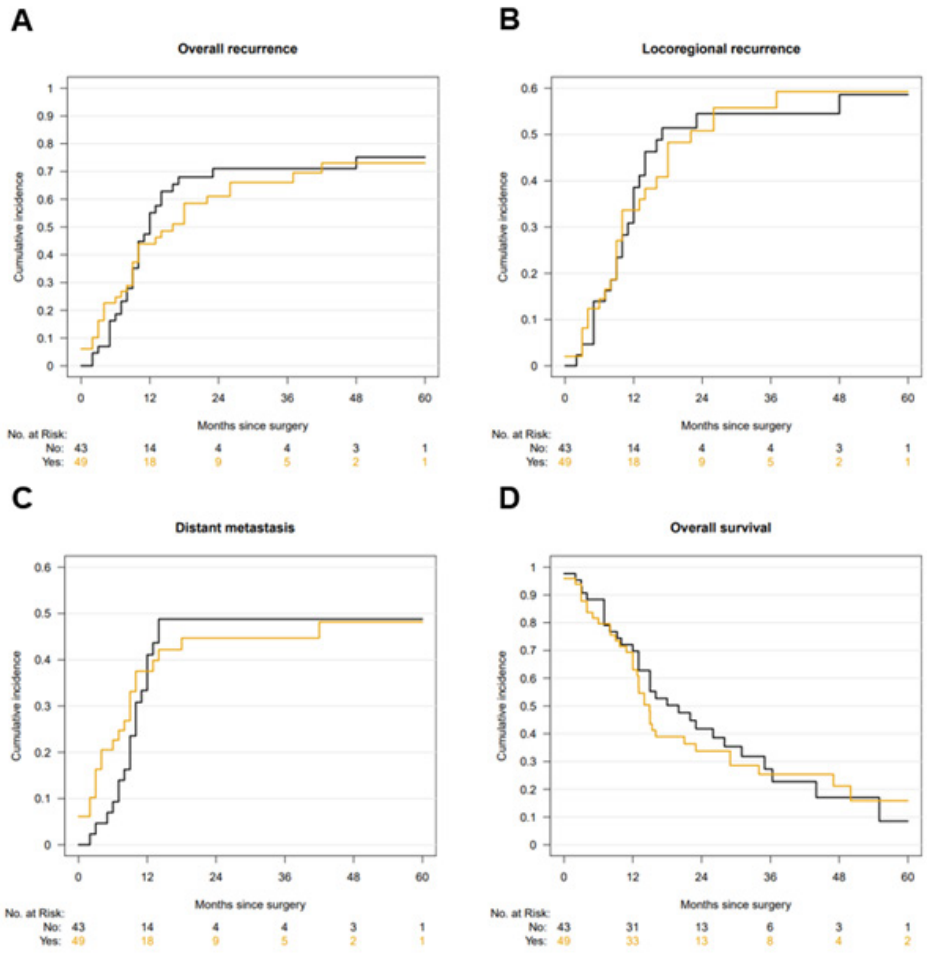

Figure 3A-D. Cumulative incidence curves by tumor invasion in resected PV-SMV (No/Yes) for (A) overall recurrence (Gray's test: P=0.76), (B) locoregional recurrence (Gray's test: P=0.97), (C) distant metastasis (Gray's test: P=0.84). (D) Kaplan-Meier curve of overall survival by tumor invasion in resected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

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

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

Table 4. Continued

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

DISCUSSION

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

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

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

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

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

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

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

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

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SUPPLEMENTARY

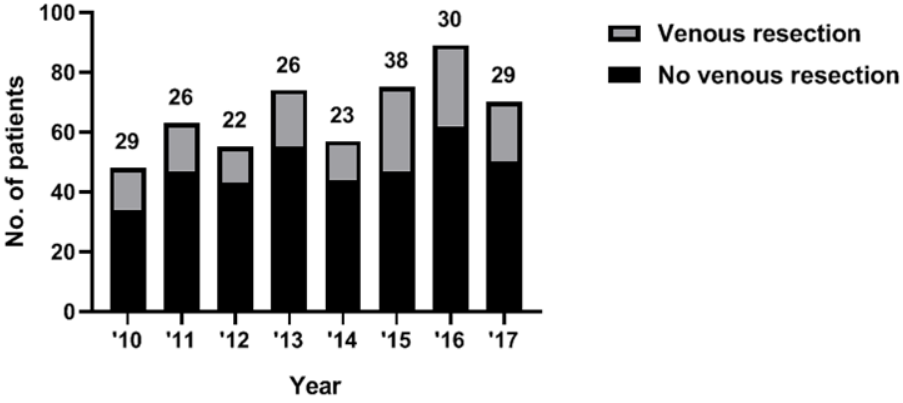

Figure S1. Volume of venous resection over the study period (numbers above bars indicate the percentage of venous resection)($P = 0.31$).