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ORIGINAL ARTICLE

Prognostic factors after pancreatoduodenectomy with en bloc portal venous resection for pancreatic cancer

Hryhoriy Lapshyn[1,2] · Peter Bronsert[3,4] · Louisa Bolm[2] · Martin Werner[3,4,5] · Ulrich T. Hopt[1,4] · Frank Makowiec[1,4] · Uwe A. Wittel[1,4] · Tobias Keck[2] · Ulrich F. Wellner[2] · Dirk Bausch[2]

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Abstract
Purpose Pancreatoduodenectomy (PD) with superior mesenteric/portal venous resection (PVR) for pancreatic ductal adenocarcinoma (PDAC) is performed routinely in case of tumor adhesion to the superior mesenteric or portal vein. True histopathological portal vein invasion (PVI) is found in a subgroup of patients. Even though this procedure has become routine in most centers for pancreatic surgery, data on prognostic factors in this situation is limited. The aim of this study was to identify prognostic factors after PD with PVR for PDAC.
Methods Retrospective analysis was performed on the basis of a prospectively maintained database, and paraffin-embedded formalin-fixed tissue slides stained for hematoxylin-eosin were re-evaluated by two independent pathologists. Statistical analysis was conducted using MedCalc software.
Results From 2001 to 2012, 86 cases of PD with PVR for PDAC with long-term follow-up and sufficient tissue for re-assessment were identified. Histopathological re-review disclosed PVI in 39 resection specimens and adhesion without infiltration in 47. Overall median survival in all patients was 22 months. Patients with PVI versus no PVI showed comparable baseline demographic and standard histopathological parameters; however, PVI was associated with microscopic hemangiosis ($p = 0.001$) and positive margin status ($p = 0.001$). Median survival in patients with PVI was 14 months versus 25 months in patients without PVI ($p = 0.042$). Only lymph node ratio and PVI were independent predictors of survival after resection.
Conclusion The only independent factors influencing overall survival after PD with PVR for PDAC were lymph node ratio and PVI. PVI might indicate aggressive tumor biology, but the available data remains controversial.

Keywords Pancreatic ductal adenocarcinoma · Pancreatoduodenectomy · Portal venous tumor infiltration · Portal venous resection · Median survival

Hryhoriy Lapshyn and Peter Bronsert share first authorship.

Ulrich F. Wellner and Dirk Bausch share senior authorship.

Hryhoriy Lapshyn, Peter Bronsert, Ulrich F. Wellner and Dirk Bausch contributed equally to this work.

✉ Ulrich T. Hopt
ulrich.hopt@uniklinik-freiburg.de

[1] Clinic for General and Visceral Surgery, University Medical Center Freiburg, Hugstetter Strasse 55, 79106 Freiburg, Germany

[2] Clinic for Surgery, University Clinic Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

[3] Institute of Surgical Pathology, University Medical Center Freiburg, Freiburg, Germany

[4] Comprehensive Cancer Center Freiburg, University Medical Center Freiburg, Freiburg, Germany

[5] German Cancer Consortium (DKTK) and Cancer Research Center (DKFZ), Heidelberg, Germany

Introduction

Involvement of the portal or superior mesenteric vein has been a determinant of borderline resectability or even irresectability of pancreatic ductal adenocarcinoma (PDAC) until the 1990s. In recent years, en bloc portal venous resection (PVR) was established as a feasible technical option during pancreatoduodenectomy (PD) to achieve negative resection margins in cases of intraoperative tumor adhesion to the vessel [1].

Current large series of PD for PDAC report PVR rates of about 30 % [2–5]. Several retrospective series conducted by specialized centers for pancreatic surgery disclosed comparable morbidity or mortality rates in PD patients with or without PVR [2–5]. A recent study report even improved survival for patients receiving PVR for tumor adhesion without histological evidence of true tumor invasion, encouraging the authors to discuss the possibility of standard PVR in all PDs for cancer [6]. There are, however, also conflicting reports, such as two large-scale analyses based on the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and National Inpatient Sample suggesting increased morbidity associated with vascular tumor involvement [7, 8]. Therefore, the indication for PVR remains controversial and parameters are needed to stratify patients according to prognosis.

The aim of this study was to assess the prognostic value of PVI as well as standard histopathological parameters in patients after PD with PVR for pancreatic cancer.

Materials and methods

Patients and operations

A retrospective analysis was performed on the basis of a prospectively maintained database. All patients undergoing PD with en bloc PVR from 2001 to 2012 at the Clinic for General and Visceral Surgery, University Medical Center Freiburg, Germany, for histologically confirmed PDAC and sufficient available tissue slides for histopathological re-evaluation were included.

Patients with encasement of the superior mesenteric or common hepatic arteries for more than 180 degrees and lack of distant metastasis were considered locally unresectable and received neoadjuvant chemoradiation with subsequent surgical exploration. This was the case in 6 of 86 patients included in this study, where only resected patients were included. Abutment of the portal venous system was not an indication for neoadjuvant therapy. Complete occlusion of the portal vein was a contraindication for resection. PVR was performed when suspected tumor infiltration of the portal vein (PV) was the only presumed barrier to negative resection margins. In case of limited tumor contact to the vein, rarely tangential clamping was performed before resection of the vessel wall. Reconstruction was performed by running suture. Vascular prostheses or vein grafts were not used in any of these cases. Standard lymphadenectomy was performed along the hepatoduodenal ligament, common hepatic artery, and portal and superior mesenteric veins and along the right aspect of the superior mesenteric artery.

Specimen workup and histopathological parameters

All resection specimens were reviewed by two experienced pathologists. Representative samples were formalin fixed and paraffin embedded (FFPE) according to a standardized protocol. In case of PV resection, the PV labeled by the surgeon was embedded in relation to the tumor and its resection margins allowing detailed pathological workup of the complete contact surface between the pancreatic tumor and the vein as well as transection margins. After processing, 4-μm-thick FFPE tissue slices were stained for hematoxylin and eosin (H&E) according to a routine protocol.

Pathological reports comprised WHO tumor type, tumor grade, pTNM classification [9], and microscopic status of the parenchymal, mesopancreatic, and bile duct resection margin, as well as the oral and aboral resection margins of the duodenum. Furthermore, the presence (1) or absence (0) of lymphatic (L), blood vessel (V), and perineural invasion (Pn) was documented. In case of the detection of equivocal tumor suspicions cells at the resection margins, immunohistochemistry for pancytokeratin was performed. For this study, all cases and H&E-stained tissue slides were re-reviewed by two experienced pathologists.

Resection margin and venous tumor infiltration

H&E-stained tissue samples of the resection margins were re-evaluated by two experienced pathologists, blinded for outcome variables. All tissue samples were histologically examined for tumor cells at the resection margins. Each resection margin was considered separately. Histopathological PVI was defined as the presence of tumor cells in the vascular tunica media (smooth muscle) or intima (Fig. 1).

Ethics and statistical analysis

Ethical permission was obtained from the local ethics committee of the University Medical Center Freiburg (Ref 13/11). MedCalc® (MedCalc Software bvba) was used for all calculations with the two-sided significance level set at $p = 0.05$. Scale variables were expressed as median and range and categorial parameters as absolute count and percentage. Univariate analysis was performed by chi-squared test for dichotomous variables, Mann-Whitney test for ordinal and rational variables, and Spearman rank test for the detection of correlation. Survival curves were plotted using the Kaplan-Meier method, and log-rank test was used to test for differences. Multivariate survival analysis was done by Cox proportional hazards models.

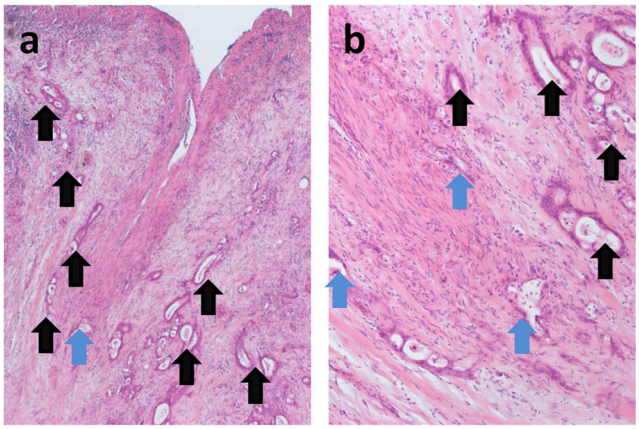

Fig. 1 Histological tumor invasion into the venous vessel wall. Tumor cells are found in the tunica media (*black arrows*) and tunica intima vena porta (*blue arrows*). Picture taken **a** at 50-fold and **b** at 100-fold magnification

Results

Baseline parameters and histopathology

Baseline patient characteristics are summarized in Table 1. From 2001 to 2012, 99 consecutive patients underwent PD with PVR for PDAC at the University Medical Center Freiburg (Freiburg, Germany). For this study, tissue slides for histopathological re-evaluation were available for 86 patients. Median age was 66 years, 44 % of patients were male, and perioperative mortality was zero. The patients were divided into two groups with regard to final pathological analysis of the surgical specimen: 39 patients (45 %) with histological tumor infiltration of the portal vein (PVI) and 47 patients (55 %) without histological PVI. The latter showed only peri-tumoral inflammation causing adherence to the venous wall. These groups with and without PVI were balanced concerning demographic and clinical parameters (Table 1).

Tumor characteristics of patients with and without PVI are also summarized in Table 1. Tumor size, grade, stage, frequency of lymphatic, and perineural invasion were comparable in the two groups. Furthermore, prevalence of nodal stage and lymph node ratio (LNR) (calculated as the number of tumor-infiltrated lymph nodes / number of retrieved lymph nodes) were similar in both patient groups. However, patients with histologically proven PVI had a significantly higher rate of R1 resections (46 %) compared to patients without PVI (15 %, $p=0.001$). In patients with margin-positive resections ($n=25$), there were $n=11$ with positive margin at the PV segment, all of whom had histopathological PV invasion ($p<0.001$ for association, Table 1). Microvascular hemangiosis (V1) was considerably more frequent in patients with relevant PVI (41.2 % compared to patients without PVI —14 %; $p<0.001$).

Table 1 Baseline and histopathology

Parameter		Total		No PVI		PVI		*p* value
		n	%	*n*	%	*n*	%	
Total		86		47		39		–
Age	<Median 66	39	45	24	51	15	38	0.243
	≥Median 66	47	55	23	49	24	62	
Sex	Female	48	56	25	53	23	59	0.591
	Male	38	44	22	47	16	41	
Neoadjuvant RCx	No	80	93	43	92	37	95	0.540
	Yes	6	7	4	9	2	5	
OP	PPPD	76	88	39	83	37	95	0.087
	Whipple	10	12	8	17	2	5	
Perioperative mortality		0	0	0	0	0	0	–
TU size	<Median 30	43	50	24	51	19	49	0.829
	≥Median 30	43	50	23	49	20	51	
T stage	T1/2	7	8	5	11	0	0	0.102
	T3/4	79	92	42	89	39	100	
LNR	<0.1	40	47	21	45	19	49	0.709
	≥0.1	46	53	26	55	20	51	
Lymphangiosis	No	45	52	25	53	20	51	0.860
	Yes	41	48	22	47	19	49	
Hemangiosis	No	70	81	44	94	26	67	0.001
	Yes	16	19	3	6	13	33	
Perineural invasion	No	31	36	17	36	14	36	0.979
	Yes	55	64	30	64	25	64	
TU grade	G1/2	54	63	33	70	21	54	0.118
	G3/4	32	37	14	30	18	46	
Margin status	Negative	61	71	40	85	21	54	0.001
	Positive	25	29	7	15	18	46	
PV margin	Negative	75	88	47	100	28	72	<0.001
	Positive	11	13	0	0	11	28	

p values given for two-sided chi-squared test

PV portal vein, *PVI* portal vein invasion, *OP* operation, *PPPD* pylorus-preserving pancreatoduodenectomy, *TU* tumor, *T stage* tumor stage, *LNR* lymph node ratio

Univariate survival analysis

Survival analysis of patients after PD with PVR is summarized in Table 2. Overall median survival for all patients was 22 months. Median survival in patients without PVI was 25 months, whereas confirmed PVI was associated with significantly shorter median survival of 14 months ($p=0.042$, see Kaplan-Meier plot in Fig. 2b). The second significant predictor of survival was the lymph node ratio (LNR). Median survival in patients with LNR <0.10 (cutoff at median) was more than two times higher (28 months) than of patients with LNR ≥0.10 (only 12 months, $p=0.003$, Fig. 2a). Median survival in patients with G1/2 was 24 months, whereas in patients with G3/4, only 14 months, constituting a statistical trend ($p=0.085$). Neoadjuvant therapy was not significantly associated with histopathological portal venous invasion. It was also no

Table 2 Survival analysis

Parameter	Condition	Survival (months)	*p* values	
			Univariate	Multivariate
Overall		22	–	
Age	<Median 66	25	0.515	0.339
	≥Median 66	18		
Sex	Female	18	0.098	0.160
	Male	24		
Neo CRx	No	18	0.219	144
	Yes	33		
OP	PPPD	22	0.789	0.926
	Whipple	13		
TU size	<Median 30	22	0.795	0.716
	≥Median 30	15		
T stage	T1/2	24	0.795	0.166
	T3/4	22		
LNR	<0.1	28	0.003	0.003
	≥0.1	12		
Lymphangiosis	No	22	0.157	0.661
	Yes	18		
Hemangiosis	No	24	0.821	0.389
	Yes	14		
Perineural invasion	No	18	0.548	0.089
	Yes	25		
TU grade	G1/2	24	0.085	0.101
	G3/4	14		
Margin status	Negative	22	0.676	0.174
	Positive	22		
PVI	Yes	14	0.042	0.040
	No	25		

Median survival derived from Kaplan-Meier method, univariate/multivariate *p* values given for two-sided log-rank test/Cox proportional hazard model

OP operation, *PPPD* pylorus-preserving pancreatoduodenectomy, *TU* tumor, *T stage* tumor stage, *LNR* lymph node ratio, *PVI* portal vein invasion, *neo CRx* neoadjuvant chemoradiation

prognostic factor in univariate or multivariate survival analysis. Survival in the PV margin positive cohort was not statistically different from other margin-positive and margin-negative patients ($p = 0.129$ and $p = 0.625$, two-sided log-rank test). Also, other demographic or standard histopathology parameters did not qualify as predictors of survival (Table 2).

Multivariate survival analysis

A multivariate analysis of tumor-related variables in 86 patients with PVR was performed to identify independently associated factors with overall survival. Only PVI and LNR, but not resection margin status; T or N stage; grading; lymphatic, microscopic blood vessel, nor perineural invasion; age; or gender were independent prognostic factors in a multivariate Cox proportional hazards model.

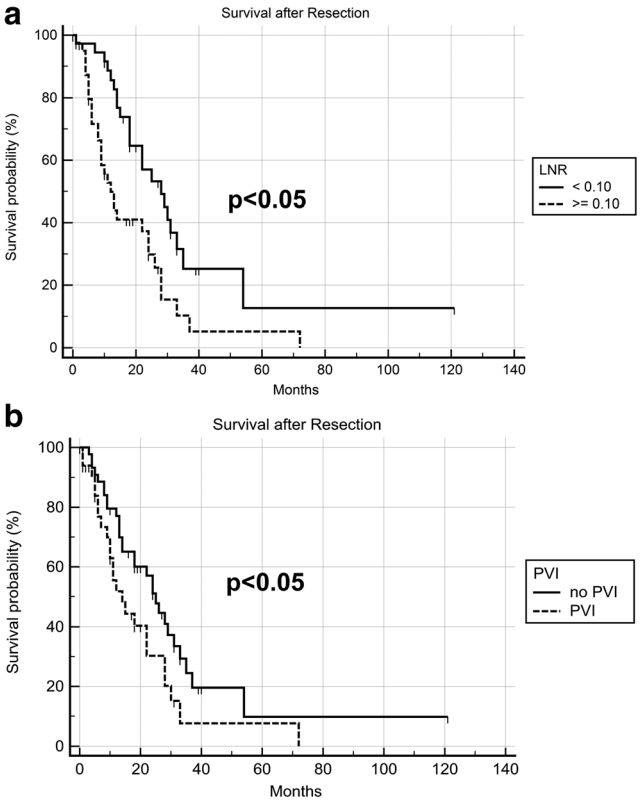

Fig. 2 Kaplan-Meier plots. **a** Survival for patients with high versus low lymph node ratio (LNR). **b** Survival for patients with histopathological versus without histopathological portal vein invasion (PVI). *p* values derived from two-sided log-rank test

Discussion

PVR for pancreatic cancer is subject to ongoing evaluations and debates. The surgical rationale for PVR during PDAC resection was established in the 1990s. Early retrospective studies assessed PVR as a feasible therapeutic option to achieve curative resection in PDAC patients with tumor adhesion to the mesenterico-PV [10, 11]. Most current series from international specialized centers and systematic reviews thereof suggest no excess morbidity or mortality after PVR [3, 5, 12–20]. However, interrogations of the ACS-NSQUIP and National Inpatient Sample databases (3582 and 10206 patients) demonstrate that vascular resection is associated with a relevant increase in overall morbidity [7, 8]. The question is therefore whether survival figures after PVR for pancreatic cancer can justify these extended resections and whether we are facing two different tumor biologies in PV-adhering or PV-invading tumors.

At present, most studies show that necessity of PVR does not negatively affect survival after resection [5, 12, 20, 21]. However, a current large retrospective multicenter study in

France [3] involving 402 patients with and 997 without PVR for pancreatic cancer demonstrates reduced survival with PVR and suggests neoadjuvant treatment as the better option to upfront surgery. Also, the currently largest single-center study from Japan found PVR to be associated with significantly reduced survival [16].

The aim of our study was to retrospectively evaluate tumors treated by PVR for heterogeneity and prognostic factors. We focused on patients with PVR for pancreatic head cancer resected from 2001 to 2012, with the prerequisite of sufficient material for valid histopathological re-evaluation and follow-up. Most other studies reporting on more than 80 cases with PVR [3, 5, 13–19] fail to report a definition of histopathological PV invasion as well as survival analysis thereof (Table 3). Consequently, only one of these studies found PVI to be a significant prognostic factor [5]. By inclusion of 86 cases with PVR, our study is currently the largest incorporating standardized histopathological re-assessment of PVI and its role as a prognostic factor. With regard to previous studies [13, 16, 17], we defined PVI as invasion of the muscular vessel wall or deeper. Thereby, only PVI and lymph node ratio were significant and independent predictors of survival.

The fact that our study did not demonstrate T-stage, grading, and R-status to be prognostic might be explained by insufficient case number. In statistical terms, the fact that PVI and lymph node ratio stand out as the only independent prognostic factors suggests that these are stronger and more important than other factors. It has also to be mentioned that existing heterogeneity in assessment of R-status and grading among other studies leads to inconsistent results [22].

Overall median survival in patients with PVI was 14 months, comparable to a recent Japanese multicenter study [5] with 15 months. One previous study demonstrates that survival in patients with PVI equals that of palliative procedures performed for unresectable disease [23], but further studies are necessary to validate this.

All patients with pancreatic cancer were routinely referred for adjuvant gemcitabine-based chemotherapy. A limitation of this study is a lack of data on how many patients successfully completed adjuvant treatment. However, as this is not a randomized study on adjuvant therapy, observed treatment effects would be expected to be biased, as only well-performing patients without complications are candidates for adjuvant therapy.

The fact that PVI and not tumor size affected survival suggests that PVI is not simply a result of long-standing local progression. PVI was significantly associated with microvascular invasion, so it might be speculated that this feature reflects a tumor-inherent propensity for invasion, a hallmark of aggressive tumor biology. Another association was observed with positive resection margin status, and positive PV margins occurred only with PVI. These observations are in line with the findings by Wang et al. [24] and compatible with the hypothesis that tumors with true PVI exhibit increased local dissemination less amenable to curative resection. However, data regarding the role of tumor topography versus biology in PVI remains scarce and controversial [24, 25].

Table 3 Studies reporting survival in $n \geqq 80$ cases of pancreatoduodenectomy with en bloc portal venous resection for pancreatic ductal adenocarcinoma and details of histopathological portal vein invasion

Author	Institution	Year	*n* PVR	PVI assessment reported	% PVI	Median survival (months) with PVR			
						Total	No PVI	PVI	*p* values
Current study	University of Freiburg, Germany	2015	86	Yes[a]	45	22	25	14	0.04
Murakami	Multicenter, Japan	2015	435	No	60	19	26	15	<0.001
Delpero	Multicenter, France	2015	402	No	NR	21	23	19	0.31
Cao	MD Anderson Cancer Center, USA	2014	94	Yes[c]	68[d]	NR	NR	NR	NR
Wang	MD Anderson Cancer Center, USA	2012	85	Yes[b]	76	18	NR	NR	0.45
Nakao	Nagoya University, Japan	2012	297	Yes[c]	36[d]	NR	NR	NR	NR
Gong	Multicenter, China	2013	119	No	96	13	NR	NR	NS
Müller	University Clinic Heidelberg, Germany	2009	110	No	78	15	NR	NR	0.65
Yekebas	University Clinic Hamburg Eppendorf, Germany	2008	100	No	77	NR	23	15	0.45
Nakao	Nagoya University, Japan	2006	200	No	57	NR	NR	NR	NR
Shimada	National Cancer Center Tokyo, Japan	2006	86	Yes[c]	55[a]	14	NR	NR	NR

PVI histologically confirmed portal venous tumor infiltration, *PVR* portal venous resection, *NR* not reported, *NS* not significant

[a] Histopathological invasion defined as invasion to the tunica media

[b] Histopathological invasion defined as invasion to tunica adventitia

[c] Histopathological invasion defined as invasion to defined as ordinal variable according to invasion depth

[d] In the subset of patients with portal vein resection

There are ongoing efforts to evaluate the role of preoperative imaging in the assessment of portal venous involvement or, more broadly speaking, borderline resectable pancreatic cancer [12, 13, 16]. Potential implications for clinical routine are substantial, including indications for upfront surgery versus neoadjuvant therapy [3]. Radiologic assessment has to be made on the basis of modern imaging techniques and detailed parameters, which should be the subject of further studies.

In summary, we present the largest cohort study of PD with en bloc PVR in pancreatic head cancer incorporating standardized histopathological re-assessment of PVI and survival analysis. Our results are suggestive of heterogeneity in tumor biology that might explain conflicting data available for PVR in the literature. The only independent predictors of survival in patients after PVR were lymph node ratio and PVI. Preoperative imaging modalities should be evaluated in their potential to discriminate between true PVI and adhesion on the way to better clarify borderline resectability.

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Authors' contributions
- Study conception and design: UFW, PB, DB, and TK
- Acquisition of data: HL, FM, PB, MW, UTH, and UAW
- Analysis and interpretation of data: HL, LB, UFW, and PB
- Drafting of manuscript: HL, LB, PB, UFW, and DB
- Critical revision of manuscript: TK, UTH, UAW, FM, MW, and DB

Compliance with ethical standards

Conflicts of interest None

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