Portal and mesenteric vein resection during pancreaticoduodenectomy and total pancreatectomy

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Background
Portal vein invasion by a malignant pancreatic mass is currently not a contraindication to pancreatic resection with acceptable oncologic outcomes.
Aim
The aim of this paper was to identify the perioperative morbidity and long-term outcomes of venous resection (VR) during pancreaticoduodenectomy (PD) and total pancreatectomy (TP) operations.
Materials and methods
We carried out a retrospective study of patients undergoing PD or TP between March 1995 and December 2014 at Mayo Clinic in Jacksonville, Florida, using data collected from an institutional review board-approved prospective database. Preoperative, operative, and postoperative clinicopathological data were collected and analyzed.
Results
Out of 601 patients who underwent PD and TP in this study, 104 (17.3%) underwent VR. The types of VR and reconstruction were as follows: type I (lateral venorrhaphy) in 49 (47.1%) patients, type II (patch graft) in 10 (9.6%) patients, type III (primary anastomosis) in 27 (26%) patients, and type IV (interposition venous graft) in 16 (15.4%) patients. Two (1.9%) patients underwent no portomesenteric reconstruction. The 90-day major postoperative complications and mortality in patients with VR were 44.2 and 7.7%, respectively, versus 29.2 and 4.4%, respectively, in patients with standard resection. The 1-year, 3-year, 5-year, and 7-year survival rates in VR with periampullary adenocarcinoma (PAAC) were 55.1, 27, 21.9, and 15.4%, respectively, whereas in patients with PAAC without VR, the survival rates were 78.4, 45.6, 34.6, and 30.9%, respectively ($P<0.01$).
Conclusion
VR and reconstruction with PD can be performed safely with acceptable perioperative morbidity and long-term survival rates to achieve complete removal of the tumor.

Keywords:
pancreaticoduodenectomy, portal vein, reconstruction, venous resection

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Introduction

Despite the current practice of a multidisciplinary team approach including advances in neoadjuvant chemotherapy and radiotherapy, 5-year survival after pancreatic resection for adenocarcinoma is still limited to 15–25% [1,2]. Involvement of major peripancreatic vessels is encountered in about half of the patients with pancreatic cancer [3,4] and the overall surgical resection rate is only 15–20% [5,6].

Complete resection of the tumor remains the only chance for cure. Invasion of the portal vein (PV) or the superior mesenteric vein (SMV) is currently not a contraindication to surgery, and vein resection and reconstruction can be performed with acceptable oncologic outcomes, almost comparable to patients who received standard resection. Given the improvements in morbidity and mortality rates, surgical resection is preferred over a bypass procedure whenever a complete tumor excision is deemed likely by preoperative and operative assessments [2,7].

The aim of the present study was to analyze the postoperative outcome and survival of patients with pancreaticoduodenectomy (PD) or total pancreatectomy (TP) and portomesenteric venous resection (VR) at our institution.

Materials and methods

A retrospective study of patients who underwent PD and TP between March 1995 to December 2014 at

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the Mayo Clinic in Jacksonville, Florida, was carried out using data collected from an institutional review board-approved prospective database.

Patients were divided into two groups: patients who underwent associated venous (portal–mesenteric) resection and those who underwent standard resection. The two groups were compared in terms of demographic features, surgical procedures, tumor pathologic findings, and perioperative outcome.

The exclusion of metastatic disease and the assessment of vascular involvement and the need for VR were determined by the preoperative imaging studies, such as enhanced computed tomography (CT) with pancreatic protocol, or MRI, and CT angiography.

The International Study Group of Pancreatic Surgery (ISGPS) guidelines and the National Comprehensive Cancer Network guidelines [8] for patients with borderline resectability were used. The tumors with borderline venous resectability include the following: (a) venous distortion of the SMV/portal venous axis in the CT scan, which may include short-segment venous occlusion with sufficient vessel length allowing reconstruction; (b) encasement of the gastroduodenal artery or even hepatic artery without extension to the celiac axis; and (c) tumor abutment of the superior mesenteric artery with less than 180° of the vessel wall circumference.

Operative strategy

PD or TP was performed either open or laparoscopically. The abdomen was explored for occult metastatic disease and the tumor was assessed for resectability. When separation of the tumor from the surrounding mesenteric vasculature was not feasible during surgery, vascular resection and reconstruction were performed to remove the tumor completely.

The ISGPS classification of VR was used as follows [8]:

(1) Type I: partial venous excision with direct closure (venorrhaphy) by suture closure.
(2) Type II: partial venous excision using a patch.
(3) Type III: segmental resection with primary veno–venous anastomosis.
(4) Type IV: segmental resection with an interposition venous conduit and at least two anastomosis.

Histopathological data on pancreatic tumor staging were collected according to the tumor, node, and metastases staging system. R1 and R2 resections were assessed at the surgical margin.

Patients with venous reconstruction received postoperative anticoagulant therapy in the form of low-molecular weight heparin and transitioned to oral Warfarin once oral intake was tolerated. After discharge, they were maintained on anticoagulant therapy for 3 months postoperatively.

All patients with VR were evaluated postoperatively for venous patency by duplex ultrasound on the same day of surgery and by CT or MRI portography within 3 weeks after the procedure. Long-term follow-up of PV patency was assessed by CT or MRI portography.

Postoperative complications within 90 days of surgery were graded [9] from 0 to 5 on the basis of the most severe postoperative complication for each patient. Grade I and II complications were considered minor and grade III, IV, and V complications were considered major. International consensus guidelines were used to evaluate complications when applicable [10,11].

The follow-up period was from the date of surgery to September 2015, with a median follow-up period 79 months. Any death during the hospital stay or within the first 90 days after surgery related to surgery was defined as perioperative mortality. Readmissions to any facility were recorded for 90 days after surgery.

Statistical analysis

Data were collected and entered into the computer using SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA) for statistical analysis. A χ^2-test or Fisher's exact test was used for qualitative variables. The Student's *t*-test and the Mann–Whitney *U*-test were used for quantitative data. Multivariable Cox regression analysis was used to determine independent predictors of mortality. A Kaplan–Meier curve was plotted for the analysis of total survival and disease-free survival and a log-rank test was used to compare the survival for both groups. The *P* value was considered statistically significant when it was less than 0.05.

Results

From March 1995 to December 2014, 601 patients underwent PD and TP for benign and malignant pancreatic diseases. Among these patients, 104 (17.3%) were treated with PD or TP combined with VR with reconstruction if appropriate. Three hundred

and fifty-five (59.1%) patients underwent PD or TP for PAAC; 87 of these patients underwent VR and reconstruction with the pancreatic resection. The demographic data and clinicopathologic findings of all patients and patients with PAAC are listed in Tables 1 and 2.

The laparoscopic approach was introduced in October 2008. A total of 305 patients (50.7%) in this series had PD and TP after this date; 152 (49.8%) of these patients underwent open surgery and 153 (50.2%) underwent laparoscopic surgery. The conversion to open surgery occurred in 28 (18.3%) patients. PV involvement of the tumor was the reason for conversion in 14 patients.

Of the 125 patients who underwent complete laparoscopic surgery, 103 (82.4%) underwent laparoscopic PD and 22 (17.6%) patients underwent laparoscopic TP.

Portomesenteric VR was performed in the 104 patients: 73 patients underwent PV resection and 31 underwent SMV resection. The resections were performed according to the ISGPS classification of vein resection, which included type I (lateral venorrhaphy) in 49 (47.1%) patients, type II (patch graft) in 10 (9.6%) patients (six from bovine pericardium graft and four from gonadal vein), type III (primary anastomosis) in 27 (26%) patients, type IV (interposition venous graft) in 16 (15.4%) patients (13 by poly tetra fluoro ethylene synthetic graft, two from gonadal vein, and one from splenic vein), and for two (1.9%) patients no portomesenteric reconstruction could be performed because of mesenteric vein thrombosis.

Eleven (10.6%) patients underwent laparoscopic VR (10 lateral venorrhaphy, one bovine pericardial batch graft).

Table 3 shows the postoperative outcome. Major postoperative complications were found in 46 (44.2%) patients with VR compared with 145 (29.2%) patients without VR ($P<0.01$).

Twenty (19.2%) patients had portal vein thrombosis (PVT) or superior mesenteric vein thrombosis (SMVT) after VR (mean: 1.8±3.1 months; range: 0.05–18 months). Eighteen (90%) patients had early PV/SMVT in the

Table 1 Patient characteristics, preoperative, and operative data for all 601 patients with pancreaticoduodenectomy and total pancreatectomy

	VR positive (*n*=104) [*n* (%)]	VR negative (*n*=497) [*n* (%)]	*P* value
Age [mean±SD (range)] (years)	66.8±11.4 (21.4–84.5)	65.5±12.1 (18.2–86.9)	0.28
Sex			
Male	53 (51)	244 (49.1)	0.73
Female	51 (49)	253 (50.9)	
Preoperative main symptoms			
Jaundice	58 (55.8)	196 (39.4)	0.01
Weight loss	64 (61.5)	245 (49.3)	0.06
Nausea/vomiting	63 (60.6)	258 (51.9)	0.4
Abdominal pain	59 (56.7)	257 (51.7)	0.35
Asymptomatic	6 (5.8)	76 (15.3)	0.01
Comorbidities			
HTN	59 (56.7)	304 (61.2)	0.81
DM	29 (27.8)	130 (26.2)	
Cardiac disease	28 (26.9)	145 (29.2)	
ASA			
I	1 (1)	1 (0.2)	0.23
II	24 (23.1)	116 (23.4)	
III	69 (66.3)	354 (71.2)	
IV	10 (9.6)	26 (5.2)	
Types of surgery			
PD	86 (82.7)	418 (84.1)	0.72
TP	18 (17.3)	79 (15.9)	
Laparoscopic	11 (10.6)	114 (22.9)	0.01
Open	93 (89.4)	383 (77.1)	
Operative time [mean±SD (range)] (min)	484±123 (219–930)	395±115 (126–824)	<0.01
Estimated blood loss [mean±SD (range)] (ml)	1592.7±2218.7 (75–18 000)	638.6±849.3 (15–7000)	<0.01
Perioperative blood transfusion [mean±SD (range)] (unit)[a]	7±11 (0–60)	2±5 (0–50)	<0.01

ASA, American Society of Anesthesiologists; CA 19-9, carbohydrate antigen 19-9; DM, diabetes mellitus; HTN, hypertension; PD, pancreaticoduodenectomy. [a]Included units during the resection and all subsequent postoperative blood transfusions.

Table 2 Patient characteristics, preoperative, and operative data in 355 patients with periampullary adenocarcinoma

	VR positive (*n*=87) [*n* (%)]	VR negative (*n*=268) [*n* (%)]	*P* value
Age [mean±SD (range)] (years)	68.1±9.2 (44.7–83.3)	68.4±10.1 (33.3–86.9)	0.82
Sex			
Male	45 (51.7)	144 (53.7)	0.74
Female	42 (48.3)	124 (46.3)	
Biliary stent	45 (51.7)	139 (51.9)	0.98
CA 19-9 [mean±SD (range)]	1619.1±6824.7 (1–45 107)	320±947 (0.9–7393)	**0.01**
Types of surgery			0.21
PD	74 (85.1)	241 (89.9)	
TP	13 (14.9)	27 (10.1)	
Laparoscopic	9 (10.3)	62 (23.1)	**0.01**
Open	78 (89.7)	206 (76.9)	
Operative time(min) Mean±SD (Range)	476±110 (219–809)	387±113 (136–819)	<**0.01**
Estimated blood loss [mean±SD (range)] (ml)	1396.1±1529.7 (75–8500)	593.9±679.2 (30–6000)	<**0.01**
Perioperative blood transfusion[a] [mean±SD (range)] (unit)	6±9 (0–55)	2±4 (0–24)	<**0.01**
Type of PAAC			
Pancreatic	82 (94.3)	170 (63.4)	<**0.01**
Bile duct	2 (2.3)	24 (9)	
Ampullary	3 (3.4)	74 (27.6)	
Duodenal	0	0	
Tumor size [mean±SD (range)] (cm)	3.5±1.8 (0.5–14)	2.9±1.7 (0.3–10)	**0.01**
Tumor stage			
T1	4 (4.6)	21 (7.8)	**0.02**
T2	7 (8)	52 (19.4)	
T3	72 (82.9)	167 (62.4)	
T4	3 (3.4)	17 (6.3)	
Unavailable	2 (1.1)	11 (4.1)	
	(*n*=82)	(*n*=170)	
Stages			0.53
IA	3 (3.7)	8 (4.7)	
IB	2 (2.4)	10 (5.9)	
IIA	16 (19.5)	38 (22.3)	
IIB	57 (69.6)	106 (62.3)	
III	1 (1.2)	3 (1.8)	
IV	1 (1.2)	2 (1.2)	
Unavailable	2 (2.4)	3 (1.8)	
Tumor grade			
Well differentiated	9 (10.3)	35 (13.1)	0.90
Moderately differentiated	45 (51.8)	133 (49.5)	
Poorly differentiated	31 (35.6)	94 (35.1)	
Unavailable	2 (2.3)	6 (2.3)	
Resection margin			
R0	66 (75.9)	236 (88.1)	**0.01**
R1/R2	21 (24.1)	32 (11.9)	
Lymph node			
N0	25 (28.7)	113 (42.2)	**0.03**
N1	62 (71.3)	155 (57.8)	
LNR [mean±SD (range)]	0.15±0.16 (0–58)	0.14±0.19 (0–1)	0.7
Lymph vessels invasion			
Yes	50 (57.5)	105 (39.2)	<**0.01**
No	37 (42.5)	163 (60.8)	
Perineural invasion			
Yes	68 (78.2)	146 (54.5)	<**0.01**
No	19 (21.8)	122 (45.5)	
Recurrence	48 (55.2)	92 (34.3)	**0.01**

ASA, American Society of Anesthesiologists; CA 19-9, carbohydrate antigen 19-9; DM, diabetes mellitus; HTN, hypertension; LNR, lymph node ratio; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; TP, total pancreatectomy; VR, venous resection.
[a]Included units during the resection and all subsequent postoperative blood transfusions. Bold values are statistically significant.

first 3 postoperative months, one patient had SMVT at 5 months, and one patient had late thrombosis at 1.5 years postoperatively, which was associated with the tumor recurrence. The estimated patency of PV after reconstruction for type I, II, III, and IV reconstruction was 91.7, 80,75, and 68.8%, respectively.

The management of PVT was conservative by anticoagulant therapy in 18 (90%) patients, surgical thrombectomy for SMVT in one patient, and tissue plasminogen activator and placement of a PV stent by interventional radiology in one patient.

Forty-eight (55.2%) of 87 patients with VR in PAAC had tumor recurrence, which was significantly higher than those undergoing resection for PAAC without VR ($P<0.01$). In the univariate analysis, there was a significant relationship between tumor recurrence and VR in PAAC ($P<0.01$).

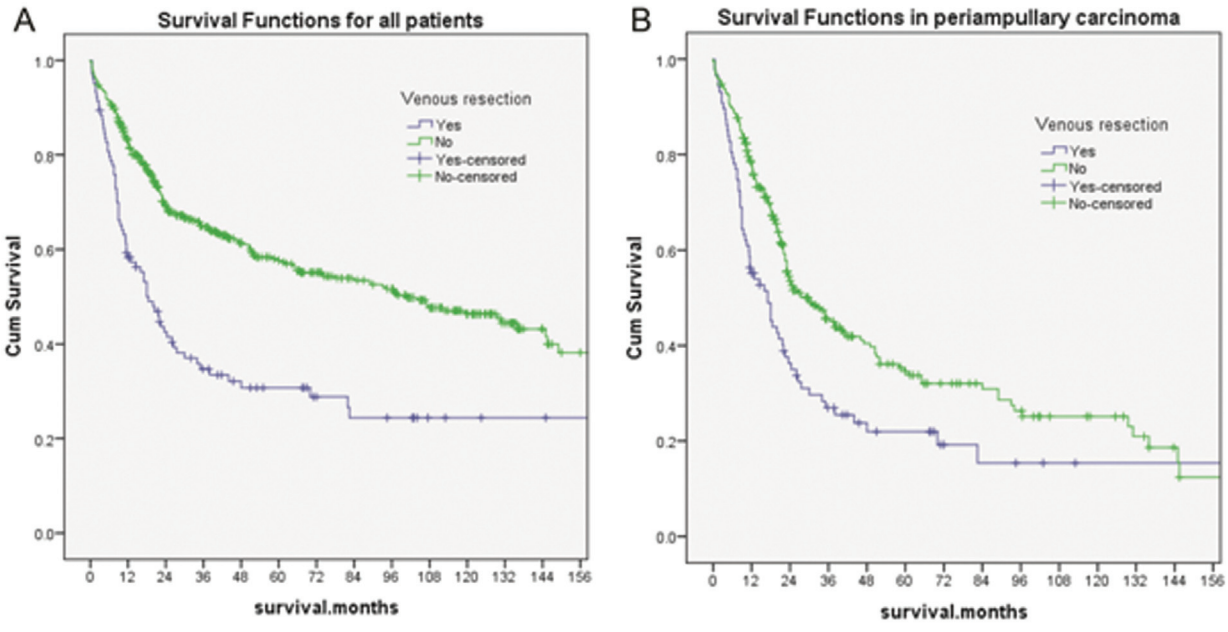
The 1-year, 3-year, 5-year, and 7-year overall total survival rates for all 601 patients were 78.6, 56.6, 52.9, and 48.4%, respectively. The 1-year, 3-year, 5-year, and 7-year total survival rates for all 104 patients with VR were 58.6, 35.3, 31.3, and 24.8%, respectively, and the 90-day perioperative mortality was eight (7.7%) patients. The 1-year, 3-year, 5-year, and 7-year survival rates for all patients without VR (497 patients) were 82.9, 65.1, 57.8, and 53.6%, respectively ($P<0.01$) (Fig. 1a).

Table 3 Postoperative data and complications

Variables	VR positive (*n*=104) [*n* (%)]	VR negative (*n*=497) [*n* (%)]	*P* value
Hospital stay [mean±SD (range)] (days)	12±13 (4–98)	11±11 (4–148)	0.28
ICU stay [mean±SD (range)] (days)	4±11 (0–59)	2±8 (0–144)	0.04
Clavien grades of complication			0.55
0	22 (21.2)	184 (37)	
I	9 (8.7)	47 (9.4)	
II	27 (26)	121 (24.3)	
IIIa	24 (23.1)	83 (16.7)	
IIIb	3 (2.9)	11 (2.2)	
IVa	2 (1.9)	9 (1.8)	
IVb	9 (8.7)	20 (4)	
V	8 (7.7)	22 (4.4)	
Rehospitalization in the first 3 months	34 (32.7)	103 (20.7)	**0.01**
Recurrence	48/78 (55.2)	92/268 (34.3)	**0.01**

VR, venous resection. Bold values are statistically significant.

Figure 1



Kaplan–Meier curve for survival. (a) Survival in all patients in our study with venous and standard resection; (b) survival in patients with periampullary adenocarcinoma with venous and standard resection

The 90-day perioperative mortality for 87 patients who underwent VR in PAAC was five (5.7%) patients. The 1-year, 3-year, 5-year, and 7-year survival rates (including the perioperative mortality) were 55.1, 27, 21.9, and 15.4%, respectively. However, in patients with PAAC without VR (268 patients), the 90-day perioperative mortality was 12 (4.5%) patients and the survival rates were 78.5, 45.9, 34.9, and 31.2%, respectively ($P<0.01$) (Fig. 1b).

In the univariate analysis, VR was a risk factor for survival ($P<0.01$), but in multivariate analysis, it was not an independent predictor of poor survival in patients with PAAC. Other independent risk factors for survival in patient with PAAC identified by multivariate analysis are listed (Table 4).

Discussion

Complete resection is the only chance for cure in patients with pancreatic cancer. Limited oncological alternatives have driven surgeons across the world to extend the operative procedures to remove PAAC with PV resection, arterial resection, other multivisceral resections, or even the resection of liver metastases in selected patients [7,12,13].

Table 4 Cox regression multivariate analysis of factors affecting long-term survival in patients with periampullary adenocarcinoma

Variables	*P*	Hazard ratio (95% confidence interval)
ECOG status	**0.001**	0.323 (0.169–0.616)
Venous resection	0.308	0.850 (0.622–1.161)
Perioperative blood transfusion	**0.001**	0.678 (0.552–0.834)
Pathological type of PAAC		
Pancreatic	0.323	0.895 (0.718–1.115)
Bile duct	0.547	1.081 (0.838–1.394)
Ampullary	0.083	1.251 (0.971–1.612)
Tumor grade		
Well differentiated	0.288	1.313 (0.794–2.171)
Moderately differentiated	0.534	0.867 (0.554–1.358)
Poorly differentiated	0.165	0.727 (0.463–1.140)
Positive margin	**0.001**	0.567 (0.400–0.804)
Positive LNs	**0.001**	0.559 (0.407–0.769)
Lymph node ratio		
0	0.855	0.063 (0–4.968)
>0 to 0.2	0.836	0.044 (0–3.468)
>0.2 to 0.4	0.830	0.038 (0–3.041)
>0.4	0.824	0.034 (0–2.715)
Lymph vessel invasion	**0.016**	0.834 (0.720–0.967)
Recurrence	**0.001**	0.407 (0.302–0.549)

ECOG, Eastern Cooperative Oncology Group; LN, lymph node; PAAC, periampullary adenocarcinoma. Bold values are statistically significant.

The morbidity, mortality, and long-term survival rates reported by many centers after VR are similar to those related to the standard surgical technique [5,14]. In our experience, major postoperative complications and mortality rates were significantly higher in the group of VR than the other group with standard surgical resection. This finding is similar to meta-analyses of a Nationwide Inpatient Sample database that included 10 206 patients who underwent pancreatectomy with VR. The study identified an increase in intraoperative and postoperative morbidity, but without an increase in mortality [15]. Ouaissi *et al.* [16] and Muller *et al.* [17] indicated that the procedure is safe, but not associated with favorable long-term survival.

In contrast to previous studies, a meta-analysis by Yu *et al.* [18] evaluating 22 retrospective studies including 2890 patients confirmed that there was no difference in perioperative morbidity and mortality rates between the two groups of patients, and these results compare favorably with that of other surgical series from high-volume single-center reviews and consensus statements published by experts around the world [5,7,14,19,20].

Beltrame *et al.* [4] reported that these differences between centers could be explained by the rate of obtaining an R0 resection [21]. In their series, the R0 resection rate was 86% in pancreatic cancer, with a median survival of 17 months versus 10 months for R1 patients. In our experience, the R0 resections rate was 75.9% in VR with PAAC, with a median survival of 28.7 versus 14.3 months for R1 and R2 patients.

In one of the previous studies [4], surgical complications occurred in 21 (33%) patients, with seven patients with pancreatic fistula, and two patients experienced PVT 11 and 13 months after the operation. The mortality rate in the group without VR was 3 versus 4% in the VR group. Overall survival was 42% at 1 year, 10% at 2 years, and 2% at 3, 4, and 5 years. In patients without evidence of vascular invasion, the overall survival was 69% at 1 year, 31% at 2 years, and 6% at 3 and 5 years versus 30% at 1 year and 0% at 2 years in patients with confirmed vascular infiltration. This survival rate is lower than that in the present series.

In another study Kulemann *et al.* [2], the overall 3-year and 5-year survival rate was 26 and 16%, respectively. In their univariate survival analysis, nodal disease, resection margin, intraoperative blood transfusions, tumor grading, and the extent of resection influenced survival. Survival after PD with PV

resection was not significantly inferior to that after standard resection.

In a previous study Al-Haddad *et al.* [22] from our institution in 2007 looking at 22 patients undergoing VR for pancreatic tumors, the 1-year and 3-year survival rates in patients with VR were 41.9 and 20% versus 1-year, 3-year, and 5-year survival rates of 64.7, 33.5, and 25% in the group that underwent pancreatic resection without VR, respectively. There was a slight survival benefit in patients who did not require VR, although this did not reach statistical significance (P=0.18).The present study has a larger number of patients and longer periods of follow-up, with nearly the same results, but with statistically a significant difference in survival (P<0.01).

In this series, six patients underwent venous reconstruction by bovine pericardium as a graft patch with good postoperative outcome and only one patient had postoperative PVT. Also, synthetic grafts such as poly tetra fluoro ethylene can be used for venous reconstruction [23,24].

Kendrick and Sclabas [25] reported that major VR with PD can be safely performed laparoscopically in selected patients. Venous reconstruction was performed in 11 patients and included primary suture venorrhaphy in four patients, patch venorrhaphy in four patients, tangential stapling in two patients, and interposition grafting using the left renal vein in one patient.

In terms of histopathological confirmation of vascular infiltration, Beltrame *et al.* [4] reported vascular invasion in 69% of cases; 86% had a negative margin (R0) and 14% had microscopic neoplastic residue (R1). The median survival was 9.5 versus 16.5 months in patients with and without histopathological reports of vascular invasion, respectively (P=0.02). The depth of tumor invasion has been shown to be a negative prognostic factor of survival. In other series, the pathology confirmed vascular invasion in 64 and 61% of cases [22,26]. Further studies are needed to evaluate the depth of vein involvement and its significance to resection.

Beltrame *et al.* [4] reported that there was a trend of better survival in the last period, as also found in our study, even though the rate of recurrence after resection was not significantly modified. This was explained by the introduction of more effective chemotherapeutic regimens (FOLFIRINOX) [27] for the treatment of relapsing tumors. There were limited data in this study on neoadjuvant and adjuvant chemoradiation therapy, and further studies are needed to examine whether multimodal treatment with a new chemotherapeutic regimen and radiotherapy [27,28] may improve the outcome after surgery in locally advanced pancreatic cancer.

Although PD or TP combined with VR and reconstruction presented a higher incidence of postoperative complications compared with standard resection, this approach can be performed safely with acceptable perioperative morbidity and mortality rates to achieve a complete removal of the tumor. The oncologic benefits of VR are still controversial, but long-term survival rates following VR for patients with PAAC are acceptable and VR can assist to accomplish a margin negative resection. A careful multispecialty evaluation and selection of patients with locally advanced tumors is recommended, and these patients should be considered for VR when feasible and when treatment can be performed at a high-volume center with experienced surgeons.

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Conflicts of interest
There are no conflicts of interest.

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