

# Venous Resection in Pancreatic Ductal Adenocarcinoma: Impact of Surgical Experience on Early Postoperative Courses

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**Abstract.** *Background/Aim:* The aim of this study was to determine the effects of surgical experience on early postoperative courses after pancreaticoduodenectomy (PD) with venous resection. *Patients and Methods:* From 2005 to 2014, 134 patients were analyzed, 62 and 72 patients were resected in periods 1 (2005-2009) and 2 (2010-2014) respectively; 115 and 19 patients underwent PD with venous resection in high- and low-volume center groups respectively. *Results:* Of the entire cohort, mortality rate was 4%. There were no significant differences between the two periods. In the low-volume center group, the mortality rate was increased (21% vs. 2%,  $p < 0.01$ ) and the mean length of hospital stay was longer (25 ( $\pm 27$ ) days vs. 17 ( $\pm 8$ ) days,  $p = 0.04$ ). The high-volume center group was the only independent protective factor regarding death (OR=0.04, 95%CI (0.01-0.38),  $p < 0.01$ ) and length of hospital stay (OR<0.01, 95%CI (0.00-0.43),  $p = 0.03$ ). *Conclusion:* Patients who present isolated venous invasion must be referred to high-volume centers for surgery.

Pancreatic ductal adenocarcinoma (PDAC) accounts for 10% of all digestive cancers (1). Only 15% of PDACs are amenable to curative therapy, consisting of complete surgical resection combined with adjuvant chemotherapy (2-6). Additionally, determining the resectability of tumors at such an early stage does not preclude rapid progression or

dissemination, resulting from aggressive tumor biology once the diagnosis has been made (7). Between 20-30% of PDACs considered resectable at imaging, are in fact locally advanced or unresectable at the time of exploratory laparotomy owing to locoregional progression or metastasis (8-10). The major goal of surgery is to achieve a radical resection (R0). The latter is achievable even in the presence of portal vein (PV) or superior mesenteric vein (SMV) invasion. The majority of patients with PV/SMV infiltration detected by initial staging (locally advanced disease) must undergo neoadjuvant therapy (6). However, for patients in whom isolated involvement of the PV/SMV was not detected at initial staging but was found intraoperatively, the optimal management is controversial; up-front surgery does not seem to be the appropriate strategy (11-13). During the last decade, there has been renewed interest in vascular resection for isolated involvement of the PV/SMV (PV/SMV-resection) in PDAC; however, there have been conflicting results according to the postoperative course as well as the impact on survival. Some studies have reported comparable complications and survival rates between standard pancreaticoduodenectomy (PD) and PD with PV/SMV-resection (14-20). Conversely, other studies have reported increased morbidity with no survival benefit for patients undergoing PD with PV/SMV-resection (6, 13, 21-23). Moreover, there is strong evidence that a center's volume and team focus (surgeons, endoscopists, radiologists and pathologists) remain an important determinant of overall mortality, postoperative outcomes, in hospital length of stay and costs of pancreatic surgery (24-30). Nonetheless, the impact of either the experience of the team focused on vascular resection or hospital volume have not been clearly established for PV/SMV-resection associated with PD.

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*Key Words:* Pancreaticoduodenectomy, venous resection, high-volume center, surgical experience, mortality.

The aim of this study was to determine the effects of the experience of teams focused on vascular resection and the center's volume on the early postoperative courses in patients undergoing PD with PV/SMV-resection for PDAC.

## Patients and Methods

*Design, setting, and patients.* From January 2005 to December 2014, 134 patients underwent PD with PV/SMV-resection for PDAC at the Marseille University Hospital group associating four centers specializing in pancreatic surgery. Data were obtained by a retrospective review of a prospectively collected clinical database. Supplemental data for this study were obtained by office and electronic medical record reviews. To determine the impact of surgical experience and the center's volume on venous resection/reconstruction, we subsequently assessed two periods and two groups. Indeed, 2010 was a turning point for the four centers with team focused on pancreatic surgery. Thus, the first period spanned from 2005 to 2009 (62 PD with PV/SMV-resection), and the second period started in 2010 until 2014 (72 PD with PV/SMV-resection). We also distinguished two centers who performed five or more PD with PV/SMV-resection per year (115 PD with PV/SMV resection were achieved in these two centers; the high volume center group) and the two others performed fewer than five procedures per year (19 PD with PV/SMV resection were achieved in these two centers; the low volume center group). Patients with metastasis or carcinomatosis were excluded from the present study.

*Preoperative evaluation.* Pancreatic tumors were assessed using preoperative computed tomographic (CT) scans performed in the previous four weeks. Magnetic resonance imaging, endoscopic ultrasound and laparoscopy were performed on an individual patient basis according to the multidisciplinary team discussion. A pancreatic tumor was defined as locally advanced when there was PV/SMV invasion, encasement or abutment of the superior mesenteric artery (SMA) or celiac trunk (12); these patients received neoadjuvant treatment according to center/physician preference. At restaging, patients who had isolated PV/SMV infiltration and in whom venous reconstruction was determined to be feasible underwent explorative laparotomy for resection. In patients with supposedly resectable PDAC at the initial staging and with isolated PV/SMV involvement found intraoperatively, no standard treatment has been accepted; interruption of laparotomy and neoadjuvant treatment or up-front venous resection was performed according to surgeon/center preferences.

*Surgical data.* PD with PV/SMV-resection surgeries were performed by experienced surgeons who had executed a mean of 20 or more PDs per year, with or without venous resection. In two of the centers, a vascular surgeon was recruited during the surgery to perform the venous resection. PD with PV/SMV-resection surgeries were performed through a large transversal laparotomy. After a thorough abdominal exploration, an artery-first approach determined the status of the SMA margin before an irreversible step in the dissection was made (31). Subsequently, a Kocher maneuver was performed. All anatomic dissections, including the hepatoduodenal ligament, pancreatic neck transection, duodenojejunal flexure, uncinate process of the pancreas and

mobilization of the infra pancreatic SMV, were performed before obtaining vascular control for venous resection. The pancreatic neck transection margin and common bile/hepatic duct transection margins were evaluated by frozen-section analysis, and additional tissue was resected to achieve negative margins at the two sites if the results were positive. Regional lymph nodes around the common hepatic artery, celiac trunk, hepatoduodenal ligament, as well as anterior and posterior pancreaticoduodenal areas were routinely dissected. Venous reconstruction was only performed after en-bloc resection of the head of the pancreas, duodenum, distal common bile duct, and retroperitoneal soft tissue margin were completed. Dissection of the right hemi circumference of the SMA to the right of the celiac trunk was required to obtain adequate medial clearance. In some cases, the section of the splenic vein from the right side of the PV gave privileged access to the right hemi circumference of the SMA, which made the dissection faster to perform, prior to the en-bloc removal of the pathological specimen with PV/SMV resection. The SMA was not routinely clamped; a simple venous suture was performed on patients undergoing lateral venous resection (LVR). The latter was performed transversally to ultimately avoid vein narrowing. If the transversal venous suture led to venous stenosis, a segmental venous resection (SVR) was performed. In the case of SVR, after mobilization of the mesenteric root, reconstruction was performed with a primary end-to-end anastomosis. Whenever a tension-free anastomosis was impossible despite complete mobilization of the mesenteric root, a venous or a prosthetic bypass was achieved. No curative anti-coagulation regimen was used postoperatively, except when a venous or a prosthetic bypass was achieved. In our study, a prophylactic anti-coagulation was the standard of care in the postoperative period, to prevent a venous thrombotic event. Extended resection was defined as a PD associated with any of the following organs involved in continuity: more than the distal half of the stomach; colon and/or mesocolon with relevant vascular structures of the transverse mesocolon (ileocolic, right, middle or left colic vessels); small bowel beyond the first segment of the jejunum; adrenal gland; kidney and/or its vasculature; and liver. The aim of this surgical procedure was to achieve a free margin resection.

*Pathological examination.* The collected data included tumor size and grading, lymphovascular and perineural invasion, and resection margin status. Tumors were graded according to the seventh edition of the American Joint Committee on Cancer staging manual (32). Serial slicing of the entire pancreatic head specimen was performed in a single axial plane according the Royal College of Pathologists and the Leeds Pathology Protocol guidelines (33, 34). The surgeon clearly identified the margins in the operative room with multicolor coded ink. The posterior margin was inked in yellow; the PV-SMV margin was inked in blue, and the SMA margin in red. The venous segment was clearly identified on the specimen. That way, large slices were obtained, allowing for a precise study of each inked margin. A positive margin was defined as a tumor present within 1.5 mm (35, 36).

*Outcomes.* Postoperative mortality included all deaths occurring prior to hospital discharge or within 30 days of the surgery. Morbidity included all complications following surgery until discharge and/or readmission within 90 days and was graded according to the Dindo-Clavien classification. Severe morbidity included Dindo-Clavien grade 3 and 4. PSCs included postoperative

pancreatic fistula (POPF), bile leak, postoperative hemorrhage, intra-abdominal abscess and delayed gastric emptying (DGE). POPF and hemorrhage were defined according to the International Study Group of Pancreatic Surgery (ISGPS), pancreatic stump leak included fistulas and fluid collections. Grades B and C POPF were defined as clinical relevant POPF. Bile leak was defined as a bilious drainage from drains or bile collection requiring drainage. DGE was defined and classified based on the ISGPS. Duration of gastric decompression and oral intake were at the discretion of the surgical team. The length of hospital stay was calculated as the number of days from surgery to the date of discharge, and the 90 days readmission rate was noted.

*Statistical analysis.* Continuous variables are expressed as means±standard deviation (SD), categorical variables are expressed as numbers and percentages. Differences between periods and groups in terms of demographic characteristics, procedures, morbidity, and mortality were measured using a chi-squared test or Fisher’s exact test for categorical data and Student’s *t*-test for continuous data, as appropriate. The whole population was used in the primary analysis. A descriptive analysis was performed. All variables with a *p*-value<0.05 were included in the multivariate model. A *p*-value <0.05 was considered to be significant. The analysis was performed using R Studio version 0.99.486.

**Results**

*Clinical characteristics, surgery and postoperative outcomes.* Clinicopathological characteristics, surgery and postoperative outcomes are summarized in Table I. Among the 134 patients who underwent PD with PV/SMV-resection for PDAC, 44 (33%) received a neoadjuvant therapy, and 68 (51%) underwent preoperative biliary stenting. Mean tumor size was 35 mm (±17 mm), and the R1 resection rate and N1 status rate were 60% and 69%, respectively. Sixty patients (45%) had histological venous wall invasion.

Seventy-seven percent of patients (n=103) underwent SVR; the main venous reconstruction was an end-to-end venous anastomosis. Total venous clamping was necessary in 84% of patients (n=112), and arterial clamping of the SMA was associated with total venous clamping in 14% of patients (n=19). The mean operative time was 469 minutes (±166 minutes), and 20% of patients (n=27) underwent intraoperative blood transfusion. According to the postoperative outcomes, the mortality and severe morbidity (*i.e.* Clavien-Dindo grade 3 or 4) rates were 4% (n=6) and 30% (n=40), respectively. All deaths were secondary to multi-visceral and cardiac failure in patients who experienced grade C POPF and postoperative hemorrhage. Clinical relevant POPF (grade B/C) occurred in 25% of patients (n=33), 8% of patients (n=11) had postoperative hemorrhage. Eight patients (6%) underwent relaparotomy for early postoperative hemorrhage or drainage of an intra-abdominal collection. DGE occurred in 44% of patients (n=59). The mean length of hospital stay was 19 days (±13 days), and the 90-day readmission rate was 16% (n=21).

Table I. *Demographics, procedure characteristics, histopathological findings and postoperative outcomes.*

	No of patients	
Characteristics		
n	134	
Female	70	(52%)
Age (years), mean (±SD)	65	(±10)
Neoadjuvant therapy	44	(33%)
Chemotherapy	42	(31%)
Radiotherapy	24	(18%)
Folfirinox	20	(15%)
Biliary stenting	68	(51%)
Histopathology		
Tumoral size (mm), mean (±SD)	35	(±17)
N1 status	93	(69%)
R1 status	81	(60%)
Lymph nodes analysed (n), mean (±SD)	17	(±8)
Lymph nodes involved (n), mean (±SD)	2	(±3)
Lymph nodes ratio, mean (±SD)	0.15	(±0.16)
Perineural invasion	103	(77%)
Venous wall invasion	60	(45%)
Surgical data		
Operative time (min), mean (±SD)	469	(±166)
Extended resection	26	(19%)
Soft pancreatic gland	28	(21%)
MPD stenting	42	(31%)
Pancreaticojejunostomy	111	(83%)
Pancreaticogastrostomy	23	(17%)
LVR	31	(23%)
SVR	103	(77%)
Total venous clamping	112	(84%)
Venous clamping duration (min), mean (±SD)	19	(±10)
Arterial clamping	19	(14%)
Length of venous resection (mm), mean (±SD)	21	(±9)
Autologous venous graft	2	(1%)
Prosthetic graft	3	(2%)
Blood transfusion	27	(20%)
Blood transfusion units ≥2	21	(16%)
Postoperative outcomes		
Overall morbidity	85	(63%)
Severe morbidity	40	(30%)
Mortality	6	(4%)
PSCs	71	(53%)
Clinical relevant POPF	33	(25%)
Bile leak	3	(2%)
Hemorrhage	11	(8%)
DGE	59	(44%)
Relaparotomy	8	(6%)
Length of hospital stay (day), mean (±SD)	19	(±13)
90 days readmission	21	(16%)

MPD: Main pancreatic duct; LVR: lateral venous resection; SVR: segmental venous resection; PSCs: pancreatic specific complications; POPF: postoperative pancreatic fistula; DGE: delayed gastric empty.

*Impact of the experience of the team focused on vascular resection (comparison of the two periods).* Univariate analyses between period 1 (2005-2009) and period 2 (2010-2014) are summarized in Table II. The preoperative biliary stenting rate

Table II. Demographics, procedure characteristics, histopathological findings and postoperative outcomes according to periods.

	2005-2009		2010-2014		p-Values
<b>Characteristics</b>					
n	62		72		
Female	26	(42%)	42	(58%)	0.24
Age (years), mean (±SD)	63	(±10)	65	(±12)	0.70
Neoadjuvant therapy	18	(29%)	26	(36%)	0.46
Chemotherapy	18	(29%)	26	(36%)	0.46
Radiotherapy	17	(27%)	7	(10%)	0.01
Folfirinox	0	(0%)	20	(28%)	<0.01
Biliary stenting	25	(40%)	43	(60%)	0.04
<b>Histopathology</b>					
Tumoral size (mm), mean (±SD)	35	(±15)	34	(±18)	0.79
N1 status	42	(68%)	51	(71%)	0.71
R1 status	39	(63%)	42	(58%)	0.60
Lymph nodes analysed (n), mean (±SD)	17	(±9)	16	(±7)	0.75
Lymph nodes involved (n), mean (±SD)	2	(±3)	3	(±3)	0.77
Lymph nodes ratio, mean (±SD)	0,13	(±0.13)	0,16	(±0.18)	0.19
Perineural invasion	42	(68%)	61	(85%)	0.02
Venous wall invasion	32	(52%)	28	(39%)	0.16
<b>Procedure data</b>					
Operative time (min), mean (±SD)	426	(±168)	506	(±157)	<0.01
Extended resection	19	(31%)	7	(10%)	<0.01
Soft pancreatic gland texture	16	(26%)	12	(17%)	0.21
MPD stenting	17	(27%)	25	(35%)	0.45
Pancreaticojejunostomy	50	(81%)	61	(85%)	0.65
Pancreaticogastrostomy	12	(19%)	11	(15%)	
LVR	15	(24%)	16	(22%)	0.84
SVR	47	(76%)	56	(78%)	
Total venous clamping	51	(82%)	61	(85%)	0.82
Venous clamping duration (min), mean (±SD)	19	(±9)	19	(±11)	0.92
Arterial clamping	10	(16%)	9	(13%)	0.62
Length of venous resection (mm), mean (±SD)	18	(±7)	23	(±10)	0.11
Autologous venous graft	0	(0%)	2	(3%)	0.50
Prosthetic graft	1	(2%)	2	(3%)	1.00
Blood transfusion	17	(27%)	10	(14%)	0.06
Blood transfusion units ≥2	13	(21%)	8	(11%)	0.15
<b>Overall postoperative outcomes</b>					
Overall morbidity	39	(63%)	46	(64%)	1.00
Severe morbidity	23	(37%)	17	(24%)	0.13
Mortality	4	(6%)	2	(3%)	0.41
PSCs	37	(60%)	34	(47%)	0.17
Clinical relevant POPF	17	(27%)	16	(22%)	0.55
Bile leak	3	(5%)	0	(0%)	0.10
Hemorrhage	5	(8%)	6	(8%)	0.96
DGE	31	(50%)	28	(39%)	0.22
Relaparotomy	6	(10%)	2	(3%)	0.14
Length of hospital stay (day), mean (±SD)	19	(±10)	19	(±14)	0.99
90 days readmission	10	(16%)	11	(15%)	1.00

MPD: Main pancreatic duct; LVR: lateral venous resection; SVR: segmental venous resection; PSCs: pancreatic specific complications; POPF: postoperative pancreatic fistula; DGE: delayed gastric empty.

was higher in period 2 when compared to period 1 (60% and 40%,  $p=0.04$ ). There were no significant differences between the two periods according to the type of venous resection (*i.e.* LVR or SVR) and the intraoperative blood transfusion rate. The mean operative time was longer in period 2 (506 (±157)

minutes and 426 (±168) minutes,  $p<0.01$ ). According to the histopathological findings, only the perineural invasion rate was significantly higher in period 2 than in period 1 (85% and 68%,  $p=0.02$ ). In terms of the postoperative course, no significant differences were noted between the two periods.

Table III. Demographics, procedure characteristics, histopathological findings and postoperative outcomes according to volume center groups.

	High-volume center		Low-volume center		p-Values
<b>Characteristics</b>					
n	115		19		
Female	55	(48%)	10	(53%)	0.67
Age (years), mean (±SD)	66	(±9)	63	(±4)	0.40
Neoadjuvant therapy	39	(34%)	5	(26%)	0.61
Chemotherapy	38	(33%)	4	(21%)	0.42
Radiotherapy	22	(19%)	2	(11%)	0.52
Folfirinox	18	(16%)	2	(11%)	0.74
Biliary stenting	60	(52%)	8	(42%)	0.47
<b>Histopathology</b>					
Tumoral size (mm), mean (±SD)	35	(±17)	31	(±11)	0.28
N1 status	79	(69%)	14	(74%)	0.79
R1 status	71	(62%)	10	(53%)	0.46
Lymph nodes analysed (n), mean (±SD)	17	(±8)	14	(±7)	0.11
Lymph nodes involved (n), mean (±SD)	2	(±3)	3	(±4)	0.71
Lymph nodes ratio, mean (±SD)	0,14	(±0.14)	0,19	(±0.23)	0.15
Perineural invasion	94	(82%)	9	(47%)	<0.01
Venous wall invasion	50	(43%)	10	(53%)	0.47
<b>Surgical data</b>					
Operative time (min), mean (±SD)	481	(±172)	397	(±108)	<0.01
Extended resection	25	(22%)	1	(5%)	0.12
Soft pancreatic gland	18	(16%)	10	(53%)	<0.01
MPD stenting	37	(32%)	5	(26%)	0.79
Pancreaticojejunostomy	97	(84%)	18	(95%)	0.19
Pancreaticogastrostomy	22	(19%)	1	(5%)	
LVR	21	(18%)	10	(53%)	<0.01
SVR	94	(82%)	9	(47%)	
Venous clamping	103	(90%)	9	(47%)	<0.01
Venous clamping duration (min), mean (±SD)	19	(±10)	25	(±7)	0.42
Arterial clamping	19	(17%)	0	(0%)	0.07
Length of venous resection (mm), mean (±SD)	21	(±9)	18	(±10)	0.58
Autologous venous graft	2	(2%)	0	(0%)	1.00
Prosthetic graft	2	(2%)	1	(5%)	0.37
Blood transfusion	15	(13%)	12	(63%)	<0.01
Blood transfusion units ≥2	12	(10%)	10	(53%)	<0.01
<b>Postoperative outcomes</b>					
Overall morbidity	73	(63%)	12	(63%)	0.38
Severe morbidity	32	(28%)	8	(43%)	0.28
Mortality	2	(2%)	4	(21%)	<0.01
PSCs	57	(50%)	14	(74%)	0.08
Clinical relevant POPF	26	(23%)	7	(37%)	0.24
Bile leak	2	(2%)	1	(5%)	0.37
Hemorrhage	8	(7%)	3	(16%)	0.19
DGE	48	(42%)	11	(58%)	0.22
Relaparotomy	5	(4%)	3	(16%)	0.09
Length of hospital stay (day), mean (±SD)	17	(±8)	25	(±27)	0.04
90 days readmission	17	(15%)	4	(21%)	0.50

MPD: Main pancreatic duct; LVR: lateral venous resection; SVR: segmental venous resection; PSCs: pancreatic specific complications; POPF: postoperative pancreatic fistula; DGE: delayed gastric empty.

*Impact of the center's volume (comparison of the two groups).* Univariate analyses between the high volume center group and the low volume center group are summarized in Table III. According to the histopathological findings, only the perineural invasion rate was significantly higher in the

high volume center group than in the low volume center group (82% vs. 47%,  $p=0.01$ ). Mean operative time was significantly longer in the high-volume center group (481 (±172) minutes vs. 397 (±108) minutes,  $p<0.01$ ). Both SVR (82% vs. 47%,  $p<0.01$ ) and total venous clamping (90% vs.

47%,  $p < 0.01$ ) rates were significantly higher in the high volume center group than in the low volume center group. The intraoperative blood transfusion rate (36% vs. 13%,  $p < 0.01$ ) and intraoperative blood transfusion unit requirement  $\geq 2$  rate (53% vs. 10%,  $p < 0.01$ ) were significantly higher in the low volume center group.

The mortality rate was significantly higher in the low-volume center group than in the high volume center group (21% vs. 2%,  $p < 0.01$ ). Although there were no significant differences, a trend was noted towards an increase in the severe morbidity (43% vs. 28%,  $p = 0.28$ ) and relaparotomy (16% vs. 4%,  $p = 0.09$ ) rates in the low-volume center group compared to the high volume center group. The mean length of hospital stay was significantly higher in the low volume center group than in the high volume center group (25 ( $\pm 27$ ) days vs. 17 ( $\pm 8$ ) days,  $p = 0.04$ ).

Multivariate analyses (Table IV) identified the high-volume center group to be the only independent protective factor against death (OR=0.04, 95%CI (0.01-0.38),  $p < 0.01$ ) and reduced length of hospital stay (OR <0.01, 95%CI% (0.00-0.43),  $p = 0.03$ ). A soft pancreatic gland texture was the only independent predictive factor of severe morbidity (OR=3.57, 95%CI% (1.43-8.92),  $p < 0.01$ ).

## Discussion

Although recent advances in surgical techniques and perioperative cares have resulted in a mortality rate below 5% for pancreatic surgery (37-40), the morbidity rate remains high, ranging from 20 to 60%, including 20% to 30% Clavien-Dindo grade 3 to 4 complications (41-45). There is strong evidence that the center's volume in pancreatic surgery and the team focus on, remain an important determinant of overall mortality and postoperative courses (24-30), and recent studies have reported increased morbidity for patients undergoing PD with PV/SMV-resection (6, 22, 23). In our study, we collected a prospective series of PD with PV/SMV-resection for locally advanced PDAC. The overall mortality and morbidity rates were 4% and 63%, respectively, including 30% Clavien-Dindo grade 3 to 4 complications, and were in accordance to the literature. We showed that, over the last decade, there were no significant differences between the two periods according to the postoperative course. However, we showed that a high volume center regarding pancreatic surgery and venous resection was identified as the only independent protective factor for death and shorter length of hospital stay.

*Preoperative management.* In our study, 51% of patients underwent preoperative biliary stenting. The preoperative biliary stenting rate was significantly higher in period 2 than in period 1, but did not differ between high volume centers and low volume centers. These results relate to recent changes in the preoperative management of patients who present

Table IV. Diagnostic value of clinical and surgical factors of death, severe morbidity, pancreatic specific complications, relaparotomy and hospital length of stay greater than 3 weeks.

	Odd Ratio	95%CI	p-Value
<b>Mortality</b>			
High volume center group	0.04	(0.01-0.38)	<0.01
Soft pancreatic gland texture	0.58	(0.07-4.63)	0.61
LVR	0.57	(0.07-4.39)	0.59
<b>Severe morbidity</b>			
High volume center group	0.79	(0.25-2.49)	0.69
Soft pancreatic gland texture	3.57	(1.43-8.92)	<0.01
LVR	0.81	(0.31-2.13)	0.67
<b>Pancreatic specific complications</b>			
High volume center group	0.40	(0.12-1.31)	0.13
Soft pancreatic gland texture	1.79	(0.71-4.50)	0.23
LVR	0.87	(0.36-2.06)	0.75
<b>Relaparotomy</b>			
High volume center group	0.52	(0.10-2.87)	0.45
Soft pancreatic gland texture	3.36	(0.70-16.04)	0.13
LVR	2.96	(0.63-13.83)	0.17
<b>Hospital length of stay greater than 3 weeks</b>			
High volume center group	<0.01	(0.00-0.43)	0.03
Soft pancreatic gland texture	88.17	(0.40-19348.54)	0.11
LVR	0.03	(0.00-5.81)	0.20

LVR: Lateral venous resection.

locally advanced PDAC. A recent multicenter study showed that serum bilirubin levels greater than 300  $\mu\text{mol/L}$  have a negative effect on survival, postoperative morbidity, and is associated with a higher rate of grade 3 and 4 according to the Clavien-Dindo classification system (46). In 2013, a literature review showed that biliary drainage was not a routine practice, and it should be recommended for patients with prolonged jaundice, biliary sepsis, renal failure or malnutrition, requiring neoadjuvant therapy before surgery (47).

Surprisingly, we observed that only one third of patients received neoadjuvant treatment when venous invasion was detected intraoperatively. Improvements in PDAC CT-scan evaluations by radiologists might lead to a higher initial staging detection rate of venous involvement. Thus, an increase in patients who received neoadjuvant treatment should have been noted in period 2. We hypothesized that, during the period of inclusion, limited venous invasion (<180°) detected by CT scan was not an indication of neoadjuvant treatment; nowadays, we observe that neoadjuvant treatment is used to avoid up-front surgery in patients with limited venous contact (13).

Neoadjuvant therapy, using a single drug or a combination of drugs, with or without radiation, has been proposed to increase the proportion of resectable tumors and decrease the

rate of margin-positive resection, as well as nodal and venous invasion (23, 48-54). Several studies have shown that a high percentage of patients who underwent surgery after neoadjuvant FOLFIRINOX therapy had an R0 resection (55-57). Recently, current national treatment guidelines for locally advanced PDAC incorporate neoadjuvant therapy, including chemotherapy and chemo-radiation (12, 58-60). FOLFIRINOX was the main neoadjuvant regimen in period 2, and was used significantly more often in period 2 than in period 1, reflecting recent changes in the preoperative oncological management of patients who present with locally advanced PDAC.

*Surgery and postoperative course.* Our study is the first to assess the effects of the center's volume on the postoperative course in patients undergoing PD with PV/SMV-resection for locally advanced PDAC. Over the last 10 years, there were no significant differences between the two periods according to postoperative course. According to the volume center groups, our study showed that a high volume of pancreatic surgery and vascular resection was identified as the only independent protective factor against death and shorter length of hospital stay. Indeed, we observed a dramatic difference in the mortality rate between centers according to the volume (21% vs. 2%,  $p < 0.01$ ). Our arbitrary criteria of more or fewer than five PV/SMV-resections seemed to be relevant and should be an indicator to discriminate centers authorized to perform vascular resection during pancreatic surgery. We supported the notion that, to be certificated to perform pancreatic surgery, pancreatic centers have to be skilled with venous resection/reconstruction given that venous involvement should not be systematically detected preoperatively. However, validation with a larger series is needed to confirm our findings.

*Histopathological findings.* There were no significant differences in tumor size and nodal status. Only the perineural invasion rate was significantly higher in period 2 and in the high volume center group. The high perineural involvement rate, both in period 2 and the high volume center group, were probably due to advances in the technical aspects of histopathological analysis. Over the last decade, histopathology teams looking for perineural involvement have developed an increased awareness of this issue, and the histological criteria constitute a negative predictor for overall survival. Several studies observed an R1 resection rate for pancreatic cancer ranging from 14% to 85% in patients who underwent PD with PV/SMV-resection, because of differing definitions of tumor invasion (6, 23, 33). Furthermore, a greater margin of clearance of at least 1.5 mm as a definition of R1 resection has been shown to further strengthen the predictive value for survival of the residual margin status (35, 36). In our study, a positive margin was defined as a

tumor present within 1.5 mm (35, 36). Within the entire cohort, the R1 margin resection and venous wall invasion rates were 60% and 45%, respectively, and were in accordance with the literature. No significant differences were noted between the two periods and the two groups.

Our study suggests that patients with locally advanced PDAC who would potentially be suitable for surgery must be referred to a high volume center with a team focused on pancreatic surgery and venous resection to improve early postoperative outcomes. A minimum of five venous resections per year seems to be relevant to dramatically reduce postoperative mortality if PV/SMV-resection/reconstruction is needed.

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Received June 6, 2017  
 Revised June 24, 2017  
 Accepted June 26, 2017