Retrospective Cohort Study

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Clinical outcomes of preservation versus resection of portal/superior mesenteric vein during pancreaticoduodenectomy in pancreatic cancer patients who respond to neoadjuvant treatment: a retrospective cohort study

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Background: R0 rates have increased as neoadjuvant treatment (NAT) has become the primary treatment for pancreatic ductal adenocarcinoma (PDAC) with venous involvement, suggesting a decrease in venous tumor infiltration. The aim of this study was to investigate the clinical outcomes of preserving the portal/superior mesenteric vein (PV/SMV) during pancreaticoduodenectomy (PD) in PDAC patients who underwent NAT.

Material and methods: The 113 patients with resectable and borderline resectable PDAC with venous involvement who responded to NAT and underwent curative PD between 2012 and 2022 were retrospectively reviewed.

Results: Among the 113 patients, PV/SMV preservation (PVP) was performed in 68 patients (60.2%), and PV/SMV resection (PVR) was performed in 45 patients (39.8%). There was no significant difference in the R0 rate, 5-year overall survival (OS) and recurrence-free survival between the two groups. PV/SMV stenosis within 3 months after surgery was more common in the PVR group than in the PVP group (1.5% versus 22.2%; $P < 0.001$), and 5-year PV/SMV stenosis-free survival was significantly higher in the PVP group than in the PVR group (76.5% versus 53.4%; $P = 0.014$). Multivariate analysis showed that gemcitabine-based neoadjuvant chemotherapy was associated with poor OS. PVR, clinically relevant postoperative pancreatic fistula, and locoregional recurrence were independent risk factors for PV/SMV stenosis.

Conclusion: The PVP group had similar oncologic outcomes and better vessel-functional outcomes than the PVR group. Therefore, if dissection is possible and there is a high likelihood of achieving R0 resection after NAT, routine PVR may be unnecessary in PDAC patients with venous involvement.

Keywords: neoadjuvant, pancreatic cancer, portal vein, stenosis, superior mesenteric vein, survival

Introduction

As R0 resection is associated with good prognosis in pancreatic cancer, the International Study Group of Pancreatic Surgery suggests that the partial resection of the portal/superior mesenteric vein (PV/SMV) should be performed to achieve curative resection in cases with suspected venous involvement[1]. Technological advancements improved our understanding of the correlation between preoperative images and vessel involvement in pancreatic cancer, expanding the indications for PV/SMV resection (PVR) during pancreaticoduodenectomy (PD)[2–7]. Nakao group classified the grades according to radiographic findings of PV/SMV involvement in pancreatic head cancer and

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showed that the actual tumor-vessel invasion rate was higher with more advanced grades of vascular contact[3]. However, the accuracy of preoperative images in predicting pathological PV/SMV invasion is not very high. For instance, histopathological findings confirmed tumor invasion of the PV/SMV in only 51–93% of patients[3,8]. Additionally, PVR is associated with an increased risk of adverse postoperative outcomes, including PV/SMV stenosis[9–13].

Neoadjuvant treatment (NAT) using chemotherapy with or without additional radiation has become the standard treatment for pancreatic ductal adenocarcinoma (PDAC) with venous involvement. NAT improves overall survival (OS) and increases the likelihood of achieving R0 resection and having negative lymph nodes compared with upfront surgery[14–17]. Therefore, PV/SMV preservation (PVP) during PD can be considered in PDAC patients with venous involvement who responded to NAT and can detach the tumor from the vessel. Some hospitals routinely perform PVR using no-touch techniques, while other hospitals attempt to dissect the vessel to preserve it. However, there is a lack of evidence on the need to perform PVR routinely in PDAC patients with improvement in the tumor-vessel relationship after NAT based on preoperative images and intraoperative findings. The aim of this study was to investigate the oncologic and vessel-functional outcomes of PVP during PD in PDAC patients who underwent NAT.

HIGHLIGHTS

- There is a lack of evidence on the need to perform portal/superior mesenteric vein (PV/SMV) resection routinely in pancreatic ductal adenocarcinoma (PDAC) patients with venous involvement who responded to neoadjuvant treatment (NAT).
- There is no significant differences in R0 rate, 5-year overall survival and recurrence-free survival between the PV/SMV preservation (PVP) group and the PV/SMV resection (PVR) group.
- The PVP group showed significantly better 5-year PV/SMV stenosis-free survival than the PVR group.
- We propose that if dissection is possible and there is a high likelihood of achieving R0 resection after NAT, routine PVR may be unnecessary in PDAC patients with venous involvement.

Material and methods

Patient selection

This study retrospectively included 264 pancreatic head cancer patients who underwent surgery after NAT between January 2012 and December 2022 at a tertiary hospital in South Korea. Clinicopathological data and radiological images were collected prospectively from electronic medical records.

Based on computed tomography (CT) and magnetic resonance imaging images, 79 patients with metastatic unresectable and locally advanced pancreatic cancer (LAPC) and 28 patients with resectable pancreatic cancer (RPC) without PV/SMV invasion were excluded. Ten patients were excluded because of cancer aggravation after NAT, such as progressive disease in the Response Evaluation Criteria In Solid Tumors[18] and aggravation of the tumor-vessel relationship. Six patients with PV/SMV encasing and long segment narrowing after NAT were excluded from the analysis because of strongly suspected vascular invasion, and all underwent PVR. Seven patients who underwent palliative surgery (open biopsy or bypass surgery) because of peritoneal seeding or liver metastasis, non-PDAC ($n=6$), death within 30 days of surgery ($n=1$), and loss to follow-up ($n=2$) and 12 patients who underwent resection for suspected main artery and adjacent organ invasion were also excluded.

Among 264 patients, we included 113 patients with resectable and borderline resectable PDAC with venous involvement who responded to NAT and underwent curative PD.

This study was conducted in compliance with the Declaration of Helsinki. This retrospective study has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS, Supplemental Digital Content 1, http://links.lww.com/JS9/D469) criteria[19].

Perioperative evaluation and surgical techniques

Tumor size and the degree of tumor-vessel contact before and after NAT were evaluated by CT or magnetic resonance imaging. Based on the extent of contact between the PV/SMV and the tumor, the resectability was classified into resectable (contact of $\leq 180°$ without contour irregularity) and borderline resectable (contact of $> 180°$ or $\leq 180°$ with contour irregularity) according to the National Comprehensive Cancer Network guideline[20]. Furthermore, the Nakao classification was reassessed, defining type A (normal), type B (unilateral narrowing of PV/SMV), and type C (bilateral narrowing of PV/SMV)[3]. For the evaluation of tumor-vessel contact, both axial and coronal images were carefully reviewed. All cases were reviewed in multidisciplinary treatment meetings, including radiologists.

PVR was performed as one of the final steps of PD, after transection of the pancreatic parenchyma and dissection of the pancreatic head plexus, at which stage the only attachment of the pancreatic head was to the PV/SMV. If the pancreatic mass attached to the PV/SMV was successfully dissected with the soft tissue layer preserved, PVP was performed without the need for additional examination. However, if the surrounding soft tissue was firm or venous tumor infiltration could not be completely ruled out even after dissection, confirmation was achieved via a frozen biopsy of the vessel groove. When PV/SMV invasion was strongly suspected and the tumor could not be detached from the vessel, the proximal and distal portions of the involved vein were clamped, and en-bloc tumor resection was performed, with both proximal and distal vessel margins checked by frozen biopsy. Reconstructive surgery included wedge resection, primary end-to-end anastomosis, and bovine patch interposition, depending on the vein involved and the extent of resection[21].

The margin status was classified as R0 or R1, with R1 defined as the presence of microscopic residual tumor when the distance between the tumor and any of the surgical margins was 0 mm, based on the final pathological report.

During postoperative follow-up, serial CT scans were performed 4 days after surgery, every 3 months until 2 years, and thereafter every 4–5 months until 5 years after surgery to evaluate for recurrence and PV/SMV stenosis. PV/SMV stenosis was defined as a reduction of more than 50% in vessel diameter compared to the first postoperative CT scan, and clinically

relevant stenosis was defined as the presence of clinical features such as bleeding or ascites, or stenoses that required interventions.

Neoadjuvant and adjuvant treatment

In our institution, most patients with RPC underwent upfront surgery. However, if the patient was reluctant to undergo surgery or had a high carbohydrate antigen 19-9 (CA 19-9) level, considered biologically borderline resectable pancreatic cancer (BRPC), or when the PV/SMV involvement was suspected, NAT was performed first. A multidisciplinary team decided whether to commence NAT, considering each patient's age, general condition, laboratory findings, and the Korean national health insurance system.

The neoadjuvant chemotherapy (NAC) regimens were FOLFIRINOX or gemcitabine-based combination. FOLFIRINOX consisted of 85 mg/m^2 oxaliplatin, followed by 400 mg/m^2 leucovorin, administered as a 2 h intravenous infusion with an additional 90 min intravenous infusion 180 mg/m^2 irinotecan after 30 min. This treatment was followed by 5-fluorouracil (FU) at a dose of 400 mg/m^2 administered as an intravenous bolus, followed by a continuous infusion of 2400 mg/m^2 for a 46 h period every 2 weeks. Gemcitabine was administered as a 30 min intravenous infusion once weekly for 3 of every 4 weeks at a dose of 1000 mg/m^2. If there was a change in regimen during NAC, patients were considered to have been treated with the main treatment regimen.

Some patients received neoadjuvant radiotherapy. Concurrent chemoradiotherapy (CCRT) with intravenous gemcitabine or 5-FU, radiation at 44–58 Gy was delivered in 28 fractions. Recently, stereotactic body radiation therapy (SBRT), which consisted of 50 Gy in five fractions, was delivered after FOLFIRINOX.

Adjuvant treatment (AT) was recommended for all patients who underwent surgery. Postoperative adjuvant chemotherapy was basically applied for 6 months with the same regimen as the NAC protocol. However, some patients did not receive AT because of their performance status or recovery after surgery.

Statistical analysis

All statistical analyses were performed using SPSS version 27.0 (IBM Corp.) for Windows. Categorical variables were analyzed using the χ^2 test and Fisher's exact test, and continuous variables were analyzed using Student's *t*-test. OS, recurrence-free survival (RFS), and PV/SMV stenosis-free survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox proportional hazard analysis was used to find independent prognostic factors for survival and logistic regression analysis was used to identify independent risk factors for PV/SMV stenosis. Variables with $P < 0.15$ in the univariate analysis were included in the multivariate model. *P* values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

The mean age was 61.3 ± 9.6 years, and 60 patients (53.1%) were male. FOLFIRINOX and gemcitabine-based NAT was administered to 94 (83.2%) and 19 (16.8%) patients, respectively. Seventy-one patients (62.8%) underwent preoperative radiotherapy of which 58 (81.7%) underwent SBRT and 13 (18.3%) underwent CCRT. One hundred-four patients (92%) underwent R0 resection, and 108 (95.6%) underwent adjuvant chemotherapy. PVP and PVR were performed in 68 (60.2%) and 45 patients (39.8%), respectively.

The baseline, surgical, and perioperative characteristics of our patients are shown in Table 1. The PVR group had a larger clinical tumor size and higher venous involvement (angle of tumor-vessel contact and according to the Nakao classification) after NAT. Other than that, there were no demographic differences, including resectability, tumor marker, NAT and AT ratio between two groups. The PVR group had a higher pathological T stage. However, there was no significant between-group difference in 30-day major morbidity, defined as Clavien–Dindo grade ≥ III[22], including clinically relevant postoperative pancreatic fistula (CR-POPF)[23], R0, and recurrence rate. Nonetheless, the PVR group had a higher incidence of postoperative PV/SMV stenosis (12 of 68 [17.6%] vs 16 of 45 [35.6%], $P = 0.031$) and clinically relevant stenosis (2 of 68 [2.9%] vs 7 of 45 [15.6%], $P = 0.015$) than the PVP group.

Long-term oncologic outcomes

The median follow-up period was 29.9 months in the entire cohort. OS and RFS rates according to PVR are shown in Figure 1. The 2-year and 5-year OS rates were 78.7 and 43.7% in the PVP group and 69.9 and 48.6% in the PVR group. There were no significant between-group differences in OS (median, 50.5 vs 49.8 months; $P = 0.956$) and RFS (median, 19.6 vs 25.3 months; $P = 0.830$) (Fig. 1A, B).

Among the 45 patients with PVR, 24 (53.3%) had inflammation, resulting in 'false negative' resection (PVR pv0). There was no significant difference in perioperative outcomes (major morbidity, R0 rate, and recurrence pattern) between the PVP and PVR pv0 groups (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D470). Furthermore, there was no significant difference in 5-year OS (43.7% versus 64.4%; median, 50.5 vs not applicable months; $P = 0.262$) and RFS (median, 19.6 vs 33.3 months; $P = 0.417$) between the PVP and PVR pv0 groups (Supplementary Fig 1, Supplemental Digital Content 3, http://links.lww.com/JS9/D471).

The multivariate analysis of the prognostic factors for OS is shown in Table 2. The gemcitabine-based NAC was significantly associated with poor OS [hazard ratio (HR) 2.03, 95% CI: 1.05–3.90; $P = 0.034$].

Causes and timing of PV/SMV stenosis

After a median CT follow-up of 21 months, 28 of 113 patients (24.8%) showed PV/SMV stenosis, with 9 of these 28 patients (32.1%) developing clinically relevant stenosis. The main causes of PV/SMV stenosis were locoregional recurrence (13 of 28, 46.4%) around the PV/SMV and postoperative changes (15 of 28, 53.6%), such as granulation tissue formation without recurrence. As it is difficult to distinguish postoperative granulation tissue from early local recurrence, serial CT images were analyzed with a shorter follow-up period to assess changes in soft tissue density around the PV/SMV in conjunction with other evidence of tumor recurrence. In the PVP group, 8 of 12 patients (66.7%) developed PV/SMV stenosis due to locoregional recurrence, while 4 of 12 (33.3%) developed it as a result of postoperative changes. In the PVR group, locoregional recurrence

Table 1

Baseline, surgical, and perioperative characteristics of PVP group and PVR group.

	Preservation of PV/SMV (PVP), $n=68$	Resection of PV/SMV (PVR), $n=45$	*P*
Age(years), mean ± SD	62.2 ± 9.6	60.6 ± 9.6	0.378
Sex ratio (M:F)	36:32	24:21	0.967
Clinical tumor size (cm), mean ± SD			
Initial	2.6 ± 0.7	3.0 ± 0.6	0.005
After NAT	1.9 ± 0.5	2.2 ± 0.7	0.024
Resectability (R/BR), *n*			
Initial	26/42	15/30	0.596
After NAT	59/9	36/9	0.336
Angle of TVC (°), mean ± SD			
Initial	135.0 ± 56.0	146.7 ± 57.3	0.286
After NAT	69.4 ± 50.2	96.1 ± 30.0	0.002
*Nakao classification (Type A/B/C), *n*			
Initial	41/18/9	21/13 /11	0.235
After NAT	62 / 6 / 0	32 / 13 / 0	0.005
CA 19-9 (U/ml), median (IQR)			
Initial	242 (944)	639 (1325.5)	0.955
After NAT	31.8 (88)	46.3 (124.6)	0.857
Neoadjuvant chemotherapy, *n* (%)			0.771
FOLFIRINOX	56 (82.4)	38 (84.4)	
Gemcitabine-based	12 (17.6)	7 (15.6)	
Neoadjuvant radiotherapy, *n* (%)	43 (63.2)	28 (62.2)	0.913
CCRT	10 (23.3)	3 (10.7)	0.182
SBRT	33 (76.7)	25 (89.3)	
Adjuvant chemotherapy, *n* (%)	67 (98.5)	41 (91.1)	0.060
Adjuvant radiotherapy, *n* (%)	13 (19.1)	6 (13.3)	0.421
Operation method, *n* (%)			0.334
PD/PPPD	65 (95.6)	41 (91.1)	
TP	3 (4.4)	4 (8.9)	
Operation time (mins), mean ± SD	270.0 ± 74.6	318.5 ± 70.3	0.001
Estimated blood loss (ml), mean ± SD	586.3 ± 591.0	725.3 ± 642.9	0.246
Postoperative stay (days), mean ± SD	11.8 ± 5.0	12.7 ± 7.6	0.438
Major morbidity (CD ≥ III), *n* (%)	14 (20.6)	7 (15.6)	0.501
CR-POPF, *n* (%)	5 (7.7)	0 (0.0)	0.069
PV/SMV stenosis, *n* (%)	12 (17.6)	16 (35.6)	0.031
Locoregional recurrence related	8 (66.7)	5 (31.3)	0.017
Postoperative change related	4 (33.3)	11 (68.8)	
Clinical relevant PV/SMV stenosis, *n* (%)	2 (2.9)	7 (15.6)	0.015
Margin status, *n* (%)			0.768
R0	63 (92.6)	41 (91.1)	
R1	5 (7.4)	4 (8.9)	
Harvested lymph nodes (*n*), mean ± SD	21.2 ± 9.4	24.0 ± 10.4	0.126
Positive lymph nodes (*n*), mean ± SD	0.6 ± 1.0	0.8 ± 1.6	0.464
Pathological T stage, *n* (%)			0.001
ypT1	32 (47.1)	10 (22.2)	
ypT2	36 (52.9)	29 (64.4)	
ypT3	0 (0.0)	6 (13.3)	
Pathological N stage, *n* (%)			0.788
ypN0	44 (64.7)	28 (62.2)	
ypN+	24 (35.3)	17 (37.8)	
Recurrence, *n* (%)	38 (55.9)	26 (57.8)	0.842
Locoregional	7 (18.4)	11 (42.3)	0.177
Systemic	24 (63.2)	13 (50.0)	
Both	7 (18.4)	2 (7.7)	

BR, borderline resectable; CA 19-9, carbohydrate antigen 19-9; CCRT, concurrent chemoradiotherapy; CD, Clavien–Dindo classification; CR-POPF, clinically relevant postoperative pancreatic fistula; NAT, neoadjuvant treatment; PD, pancreaticoduodenectomy; PPPD, pyrolus preserving pancreaticoduodenectomy; PV/SMV, portal/superior mesenteric vein; R, resectable; SBRT, stereotactic body radiation therapy; TP, total pancreatectomy; TVC, tumor-vessel contact.

*Nakao classification: Type A: normal, Type B: unilateral narrowing of PV/SMV, Type C: bilateral narrowing of PV/SMV.

caused PV/SMV stenosis in 5 of 16 patients (31.3%), while 11 of 16 (84.6%) developed it as a result of postoperative changes. In the PVR group, the postoperative PV/SMV stenosis rate was more than twice as high as that in the PVP group (17.6% vs 35.6%), and clinically relevant stenosis was more than five times as high (2.9% vs 15.6%) (Table 1). The method of venous reconstruction was not associated with PV/SMV stenosis: 37.5% (3 of 8) for wedge resection versus 36.4% (12 of 33) for segmental

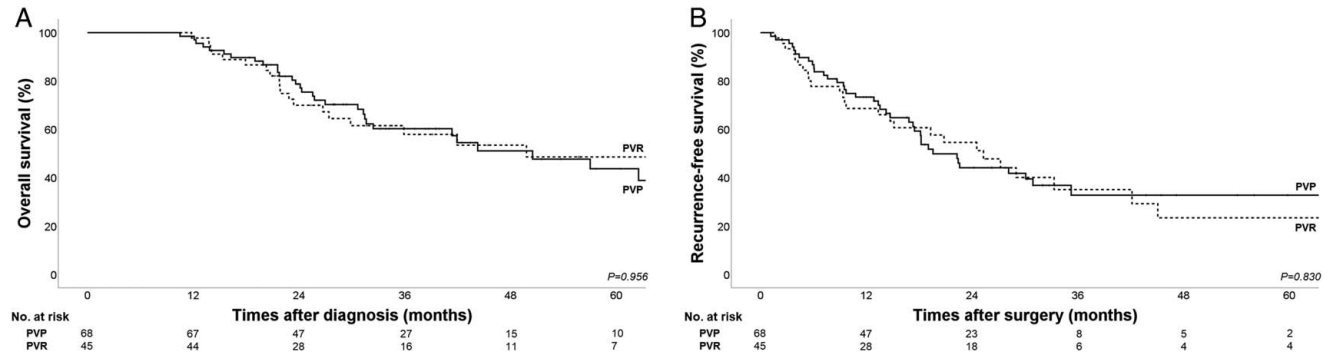

Figure 1. Kaplan -Meier curves of overall survival and recurrence-free survival in the PVP and PVR groups A. 5-year overall survival (OS) in the PVP and PVR groups (43.7% versus 48.6%; median, 50.5 vs 49.8 months; $P = 0.956$) B. 5-year postoperative recurrence-free survival (RFS) in the PVP and PVR groups (median, 19.6 vs 25.3 months; $P = 0.830$) PVP, PV/SMV preservation; PVR, PV/SMV resection; PV/SMV, portal/superior mesenteric vein.

resection and end-to-end anastomosis versus 25% (1 of 4) for bovine patch interposition ($P = 0.897$).

PV/SMV stenosis within 3 months after surgery was more common in the PVR group than in the PVP group (1 of 68 [1.5%] vs 10 of 45 [22.2%], $P < 0.001$). Most short-term stenoses (within 3 months) were caused by postoperative changes (9 of 11, 81.8%). The incidence rates of PV/SMV stenosis from 3 months to 1 year and after 1 year, in the PVP and PVR groups were 11.8% versus 6.7% and 4.4% versus 6.7%, respectively. After 3 months, there was no between-group difference in the incidence of stenosis and the leading causes of PV/SMV stenosis were locoregional recurrence (11 of 17, 64.7%) (Fig. 2A). Furthermore, 5-year PV/SMV stenosis-free survival was significantly higher in the PVP group than in the PVR group (76.5% versus 53.4%; $P = 0.014$) (Fig. 2B).

Multivariate analysis showed that PVR [odds ratio (OR) 3.17, 95% CI: 1.05–9.59; $P = 0.041$], CR-POPF (OR 21.86, 95% CI: 1.47–324.35; $P = 0.025$), and locoregional recurrence (OR 3.95, 95% CI: 1.30–11.97; $P = 0.015$) were independent risk factors for PV/SMV stenosis (Table 3).

Table 2

Prognostic factors for overall survival.

	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age (year) ≥ 70	1.45 (0.75–2.80)	0.267		
Sex				
M	1			
F	0.86 (0.49–1.51)	0.597		
Degree of tumor-vessel contact > 90				
Initial	0.59 (0.28–1.22)	0.154		
After NAT	0.94 (0.53–1.67)	0.836		
*Nakao classification (Initial)				
Type A	1			
Type B	1.14 (0.59–2.18)	0.697		
Type C	1.08 (0.50–2.31)	0.847		
*Nakao classification (after NAT)				
Type A	1			
Type B	1.59 (0.81–3.12)	0.176		
CA 19-9 > 37 U/ml				
Initial	1.10 (0.53–2.30)	0.796		
After NAT	1.13 (0.65–1.99)	0.663		
Neoadjuvant chemotherapy				
FOLFIRINOX	1			
Gemcitabine-based	2.08 (1.09–4.01)	0.028	2.03 (1.05–3.90)	0.034
Margin status				
R0	1			
R1	1.40 (0.56–3.54)	0.474		
T stage				
ypT1	1			
≥ ypT2	1.61 (0.87–2.99)	0.133	1.51 (0.80–2.83)	0.203
N stage				
ypN0	1			
ypN+	1.50 (0.85–2.64)	0.158		
Adjuvant chemotherapy	0.49 (0.15–1.16)	0.241		
Pathological vessel invasion	1.64 (0.86–3.16)	0.136	1.48 (0.76–2.88)	0.246

CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio.

*Nakao classification: Type A: normal, Type B: unilateral narrowing of PV/SMV, Type C: bilateral narrowing of PV/SMV.

Discussion

NAT is the current accepted standard treatment for patients with BRPC and LAPC. Even among cases of RPC with venous involvement, there are variations in tumor aggressiveness, which correlate with higher risks of recurrence and poorer prognosis[24,25]. While the effectiveness of NAT for patients with RPC is controversial, a recent retrospective study showed that NAT was associated with better R0 resection rate (86.3% vs 77.1%; $P = 0.004$), lymph node negativity rate (57.6% vs 34.2%; $P = 0.002$), and longer survival (median 33 vs 23 months; $P = 0.003$) in patients with resectable PDAC with venous involvement[26]. R0 rates have increased as NAT has become the primary treatment for PDAC with venous involvement, suggesting a decrease in venous tumor infiltration. It is challenging to distinguish true venous tumor infiltration from inflammation or fibrosis after NAT using preoperative images, which may not accurately show resectability[27–29]. Nonetheless, there is controversy regarding whether the PV/SMV should be resected during PD in PDAC patients who responded to NAT. While oncologic outcome after surgery is very important, postoperative vessel-functional outcome is also clinically important because PV/SMV stenosis can cause PV hypertension, potentially leading to severe complications.

NAT is associated with downstaging of the tumor. In this study, the mean clinical tumor size (cm) decreased from 2.7 to 2.0 and angle of tumor-vessel contact (°) decreased from 126 to 87 after NAT. Fourty-one patients with RPC and 72 patients with BRPC were reevaluated after NAT, with 95 patients as RPC and

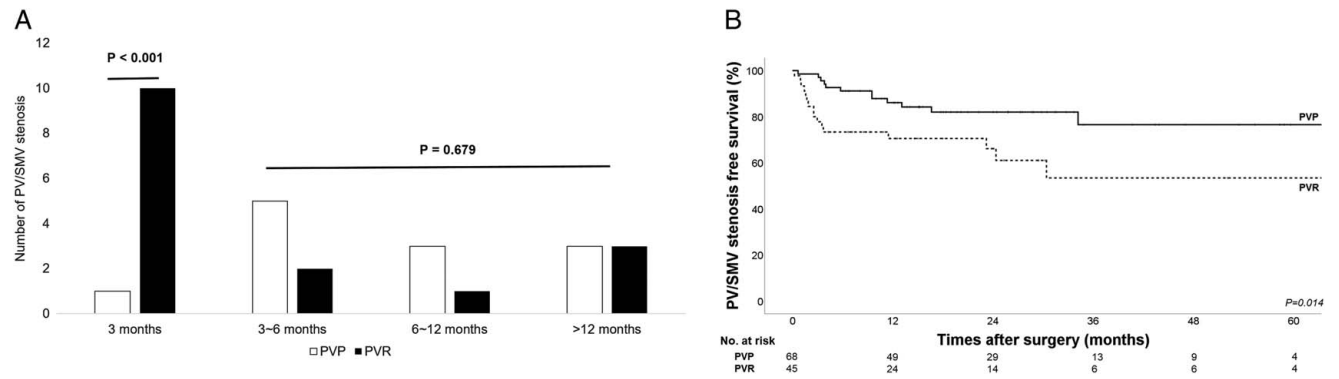

Figure 2. PV/SMV stenosis in the PVP and PVR groups. A. Time of PV/SMV stenosis occurrence in the PVP and PVR groups. B. 5-year postoperative PV/SMV stenosis-free survival in the PVP and PVR groups (76.5% versus 53.4%; $P = 0.014$) PV/SMV, portal/superior mesenteric vein; PVP, PV/SMV preservation; PVR, PV/SMV resection.

18 as BRPC. Furthermore, the ratio of Nakao classification (type A: type B: type C) changed from 62: 31: 20 to 94: 19: 0 after NAT.

We found no significant differences in R0 rates and 5-year OS and RFS between the PVP and PVR groups. As the pathological invasion of PV/SMV is a poor prognostic factor for survival[2,3,30–32], we performed additional subgroup analysis to compare oncologic outcomes between the PVP and PVR pv0 groups. There were no significant differences in R0 rates and 5-year OS and RFS between these two groups. Some studies have shown that PVR is feasible only when intraoperative findings suggest PV/SMV invasion, despite preoperative image findings suggesting PV/SMV involvement. Turrini *et al.*[33] compared clinical outcomes between PVP and PVR pv0 groups and showed that OS was significantly higher in the PVR pv0 group than in the PVP group (median, 22 vs 42 months; $P = 0.040$), suggesting that PV/SMV dissection from tumors increased the risk of noncurative resection. In contrast, Klein *et al.*[34] showed that OS was significantly worse in the PVR pv0 group than in the PVP group (median, 558 vs 311 days; $P = 0.001$), whereas Kishi *et al.* found no significant difference in RFS (median, 15.5 vs 14.7 months; $P = 0.557$) and OS (median, 32.4 vs 32.1 months; $P = 0.780$) between the PVP and PVR pv0 groups. These results suggest that extensive PVR is not always required and that PVR is needed only when the tumor cannot be detached from the vessel during surgery[35]. Given the discrepancy in the results, the potential benefit of routine PVR is debatable, and further evaluation is needed. However, in contrast to our study, these three studies evaluated patients who did not undergo NAT. As NAT provides good local control through early systemic treatment for undetected micrometastasis and increases R0 resection, a new approach is needed to determine whether to resect PV/SMV after NAT.

Table 3

Risk factors for PV/SMV stenosis.

	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (year) ≥ 70	0.75 (0.30–1.87)	0.537		
Sex				
M	1			
F	0.66 (0.28–1.58)	0.353		
Neoadjuvant radiotherapy	1.34 (0.54–3.31)	0.527		
Resection of PV/SMV	2.58 (1.08–6.16)	0.034	3.17 (1.05–9.59)	0.041
Method of venous reconstruction				
Wedge resection	1			
End-to-end anastomosis	0.91 (0.18–4.48)	0.907		
Bovine patch interposition	0.56 (0.04–8.09)	0.667		
Margin status				
R0	1			
R1	1.58 (0.37–6.78)	0.538		
Major morbidity (CD ≥ III)	2.88 (1.06–7.84)	0.038	1.54 (0.34–6.90)	0.575
CR-POPF	15.24 (1.62–143.62)	0.017	21.86 (1.47–324.35)	0.025
Locoregional recurrence	5.46 (2.12–14.09)	< 0.001	3.95 (1.30–11.97)	0.015
Adjuvant chemotherapy	0.07 (0.01–0.67)	0.021	0.1 (0.01–1.04)	0.054
Adjuvant radiotherapy	1.51 (0.51–4.44)	0.454		

CD, Clavien–Dindo classification; CR-POPF, clinically relevant postoperative pancreatic fistula; OR, odds ratio; PV/SMV, portal/superior mesenteric vein.

Our results showed that PVP was associated with better vessel-functional outcomes and PVR affects PV/SMV stenosis. Among patients with PV/SMV stenosis, the median time to stenosis caused by local recurrence, postoperative changes was 11.3 and 2.5 months, respectively ($P = 0.012$). Postoperative changes were the primary cause of PV/SMV stenosis in the PVR group (11 of 16, 68.8%), and many patients developed stenosis within 3 months after surgery (10 of 16, 62.5%). Eight of ten patients with short-term stenosis (within 3 months) developed it as a result of postoperative changes. Furthermore, the higher incidence of clinically relevant stenosis in the PVR group (2 of 12 [16.7%] vs 7 of 16 [43.8%]) seemed to be associated with postoperative changes resulting from vascular manipulations during surgery. Kang *et al.* also showed that 28 out of 55 patients (51%) who underwent PVR developed PV stenosis and 5-year PV patency rates were significantly lower than in PVP group (72.7% vs 17%; $P < 0.001$). Furthermore, among the ten patients who developed PV stenosis within the first month after surgery, nine patients underwent PVR and PVR was an independent risk factor for PV stenosis (OR 3.28, 95% CI: 1.80–6.00; $P < 0.001$) regardless of

the vascular reconstruction method[10]. Therefore, most technical problems seem to occur in the early stage after surgery, and PVR should be carefully considered as it affects vessel-functional outcomes and can induce clinically relevant stenosis, leading to PV hypertension.

In the PVP group, locoregional recurrence was the primary cause of PV/SMV stenosis (8 of 12, 66.7%). Considering that R status after PD can affect overall recurrence rates[36,37], the PV/SMV stenosis ratio may differ depending on the R status. Among the PVP group, only one patient had an R1 resection in the PV/SMV stenosis group, and there was no demographic difference in R1 resection (4 of 56 [7.1%] vs 1 of 12 [8.3%], $P = 0.886$). In multivariate analysis, R1 resection was not an independent risk factor for PV/SMV stenosis. Furthermore, there was no demographic difference in R1 resection between the PVP and PVR groups (5 of 68 [7.4%] vs 4 of 45 [8.9%], $P = 0.768$), and the same result was seen within the PV/SMV stenosis group (1 of 12 [8.3%] vs 2 of 16 [12.5%], $P = 0.724$). Therefore, there seemed to be no association between R status and PV/SMV stenosis.

Surgical technique with aggressive local dissection is critical for achieving R0 and complete tumor remnant resection, which can affect locoregional recurrence, but it has limitations. A review of prospective randomized trials concerning the value of extended surgery concludes that circumferential dissection of the SMA is no longer recommended considering its morbidity and oncological necessity[38]. In the resectable stage, however, extended dissection of perineural tissues, so called as triangular resection, may offer advantages in achieving R0 resection and reducing local recurrence. In cases of BRPC and LAPC, besides surgical extent, NAT including radiotherapy is also very important for local control. Recent reviews of SBRT have shown that it is an effective modality for patients with pancreatic cancer[39,40]. Future efforts will be needed to expand NAT using radiotherapy, which could potentially improve outcomes for pancreatic cancer patients.

The rate of pathological PV/SMV invasion (21 of 45, 46.7%) in the resected vein was lower than previously reported (51–93%). In contrast to previous studies, our study revealed no significant difference in 5-year OS (43.7% versus 30.9%; median, 50.5 vs 29.9 months; $P = 0.247$) and RFS (median, 19.6 vs 15.1 months; $P = 0.210$) when comparing the PVP and PVR pv(+) groups. These results suggested that NAT may have the effect of reducing venous tumor infiltration and extensive PVR does not compensate for the aggressive biology of PDAC, especially in the era of NAT.

In the PV/SMV invasion group, preoperative images tended to be more severe (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/D470) and often displayed asymmetric vessel contours or significant long segment narrowing of the vessels, compared to the noninvasion group, even after NAT. This information can be useful in surgical planning, including decisions on whether to attempt minimally invasive pancreatic surgery (MIPS) or to perform vessel resection. MIPS has recently been considered an important part of current pancreatic surgery practice and there is an increasing effort to implement MIPS for BRPC patients. Even though, there is insufficient evidence to define a venous resection and anastomosis technique during MIPS[41], it might be considered for patients who have responded to NAT, except in cases of extensive vessel invasion by experienced surgeons in high-volume centers. Although preoperative images can be useful in surgical planning, they may not accurately show the extent of venous tumor infiltration. Therefore, the final decision on whether to perform PVR was made based on the surgical findings; however, there is a need to better justify the subjectivity in intraoperative decision-making. As artificial intelligence is increasingly being used in medical practice and has demonstrated growing applicability, we can expect it to improve preoperative planning and operative execution in the future[42–44].

This study has several limitations. First, the experimental design was retrospective, single-center study, and selection bias could not be avoided. Second, there is still a lack of evidence regarding the effectiveness of NAT in RPC patients, and high-level evidence is still needed. Third, the absence of objective preoperative measures following NAT makes intraoperative decisions regarding PVR challenging and often subjective, varying depending on the individual surgeon. Lastly, the PVP group might have included patients with pathological venous infiltration because true venous infiltration is confirmed only following PVR. However, the R1 rate, the sites of resection margin positivity, and postoperative prognosis were similar between the two groups. Five of 68 patients (7.4%) in the PVP group had an R1 resection, and only one patient (1.5%) had margin positivity in the PV/SMV groove.

In conclusion, the PVP group had similar oncologic outcomes and better vessel-functional outcomes than the PVR group. Therefore, if dissection is possible and there is a high likelihood of achieving R0 resection after NAT, routine PVR may be unnecessary in PDAC patients with venous involvement.

Ethical approval

This study was exempted from deliberation by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB no. 2402-147-1516).

Consent

Informed consent for enrolled patients was waived by the Institutional Review Board of Seoul National University Hospital.

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Author contribution

Y.S.C.: conceptualization, formal analysis, writing – original draft, and writing – review and editing; H.-S.J.: methodology and validation; W.-G.Y. and Y.H.: investigation; Y.J.C. and M.L.: data collection; W.K. and J.S.P.: validation; J.-Y.J.: supervision and writing – review and editing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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Guarantor

Yoon Soo Chae and Jin-Young Jang.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Provenance and peer review

Not applicable.

Assistance with the study

Not applicable.

Presentation

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