Table 1 Baseline demographics

	Resectable	Borderline	*P*-value
Number of patients	582	389	–
Age (y), median (range)	68 (27–90)	65 (32–87)	<0.001
Sex (male : female)	320:262	229:160	0.23
Past medical history or Comorbid illness			
Hypertension, *n* (%)	166 (29)	92 (24)	0.091
Coronary arterial disease, *n* (%)	66 (11)	36 (11)	0.30
Diabetes mellitus, *n* (%)	175 (30)	120 (31)	0.80
Other malignancy, *n* (%)	94 (16)	41 (11)	0.012
Peptic ulcer, *n* (%)	45 (7.8)	25 (6.4)	0.44
Hepatitis, *n* (%)	39 (6.7)	20 (5.1)	0.31
Other digestive disease[a], *n* (%)	98 (17)	49 (13)	0.074
Respiratory disease, *n* (%)	41 (7.1)	20 (5.1)	0.22
Cerebral Vascular disease, *n* (%)	25 (4.3)	17 (4.4)	0.96
Jaundice, *n* (%)	190 (33)	169 (43)	<0.001
Biliary drainage, *n* (%)	187 (32)	169 (43)	<0.001
Pre-treatment serum tumor marker			
CEA (ng/ml), median (range)	3 (0–435)	3.5 (0–675)	0.0039
CA19-9 (U/ml), median (range)[b]	78 (0–47,470)	203.75 (0–220,540)	<0.001

[a] Other digestive disease included appendicitis (*n* = 47), cholecystolithiasis (*n* = 33), colonic polyps (*n* = 16), pancreatitis (*n* = 10), gastritis (*n* = 8), gastric polyps (*n* = 5), intestinal obstruction (*n* = 4), liver cirrhosis (*n* = 3), reflux esophagitis (*n* = 2), fatty liver (*n* = 2), hepatic hemangioma (*n* = 2), pancreatic cyst (*n* = 2), hemorrhoid (*n* = 2), irritable bowel disease, trauma, situs inversus, colonic derticulitis, ulcerative colitis, Peutz-Jeghers syndrome (*n* = 1), unknown (*n* = 5)

[b] The values of CA19-9 were measured after biliary drainage when the patients with jaundice

Table 2 Types of neoadjuvant therapy and agents

	Resectable	Borderline	*P*-value
Neoadjuvant therapy, *n* (%)	185 (32)	203 (52)	<0.0001
Types of therapy			
Radiotherapy, *n* (%)	114 (20)	140 (36)	<0.0001
Irradiation (Gy), median (range)	50 (35.2–54)	45 (10.8–67.5)	<0.0001
Agents provided			
With Gemcitabine	95	90	
With S1	8	28	
With Gemcitabine+S1	5	13	
With Other agents[a]	4	7	
Radiation alone	4	7	
Duration[b] (days), median (range)	99.5 (56–278)	82 (46–391)	<0.0001
Chemotherapy, *n* (%)	65 (11)	50 (13)	0.43
Agents provided			
Gemcitabine	17	22	
S1	5	2	
Gemcitabine+S1	26	24	
Gemcitabine+Other agents[c]	17	2	
Duration[b] (days), median (range)	28 (13–138)	81.5 (16–137)	0.0029
No record	6	13	

[a] Other agents was 5-FU + CDDP + MMC (*n* = 11)

[b] Duration represents the days from the start of neoadjuvant therapy to operation

[c] Other agents included 5-FU (*n* = 18) and CDDP (*n* = 1)

Table 3 Adverse events during neoadjuvant therapy

	Grade 1–4 (%)			Grade 3–4 (%)		
	Chemotherapy	Radiotherapy	*P*-value	Chemotherapy	Radiotherapy	*P*-value
Neutrocytopenia	58.8	65.4	0.30	33.8	20.0	0.0164
Leukocytopenia	53.8	75.5	0.0003	16.3	36.7	0.0007
Anemia	28.2	61.5	<0.0001	1.4	3.9	0.45
Thrombocytopenia	26.7	35.7	0.16	4.0	2.8	0.70
Fatigue	20.8	33.2	0.048	0.0	0.0	>0.99
Allergy	13.7	9.7	0.37	0.0	1.1	>0.99
Nausea/Vomiting	9.7	29.6	0.0006	1.4	2.2	>0.99
Liver dysfunction	3.1	0.4	0.055	0.0	0.0	>0.99
Pigmentation	2.3	1.8	0.70	0.0	0.0	>0.99
Anorexia	1.7	8.6	0.010	0.9	2.2	0.67
Cholangitis/Cholecystitis	0.8	2.5	0.43	0.0	2.1	0.17
Pneumonitis	0.0	2.5	0.094	0.0	1.3	0.56
Body weight loss	0.0	2.1	0.17	0.0	0.0	>0.99
Other[a]	6.1	2.5	0.93	0.0	0.0	>0.99

[a] Other non-hematological adverse events included thrombosis, peptic ulcer, oral mucositis, renal dysfunction, constipation

leukocytopenia occurred in more than half of the patients who received neoadjuvant therapy. Any grade leukocytopenia ($P = 0.0003$), anemia ($P < 0.0001$), fatigue ($P = 0.048$), nausea/vomiting ($P = 0.0006$), and anorexia ($P = 0.01$) were significantly more frequent in patients receiving chemoradiotherapy than systemic chemotherapy. Grade 3/4 neutropenia was significantly more frequent in patients receiving chemotherapy ($P = 0.0164$), whereas grade 3/4 leukocytopenia was significantly more frequent in patients receiving chemoradiotherapy ($P = 0.0007$). There were significant differences in any other AE.

Radiological tumor response to neoadjuvant therapy was assessed by tumor reduction rate, shown by waterfall chart analysis (Fig. 2). The median tumor reduction rate was 6.3% (range, –45.2–93.9%). According to Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, 16% of patients showed a partial response, 80% had stable disease, and 4% had progressive disease (PD); none had a complete response to neoadjuvant therapy. Responses to neoadjuvant therapy were similar in patients with resectable and borderline resectable tumors ($P = 0.14$).

Resectability

Of the 388 patients who received neoadjuvant treatment, 25, including eight with resectable and 17 with borderline resectable tumors, did not undergo surgery, including 21 (84%) with PD and one with an AE during preoperative treatment. Of the 582 patients with resectable disease, 397 were scheduled for surgery-first, and, of these, 375 (94.5%) underwent resection. Similarly, of the 185 patients with resectable disease who received neoadjuvant therapy, 171 (92.4%) underwent resection ($P = 0.34$). R0 resection was performed on 305 patients in the surgery-first group and 164 in the neoadjuvant group. The R0 rate was significantly higher in the neoadjuvant than in the surgery-first group, both by on-treatment ($P < 0.0001$) and intention to treat ($P = 0.0003$) analysis (Table 4a). Of the 389 patients with borderline resectable disease, 186 were scheduled to undergo surgery first, and, of these, 156 (83.9%) underwent resection. Similarly, of the 203 patients with borderline resectable disease who received neoadjuvant treatment, 156 (77.8%) underwent resection ($P = 0.16$). Curability assessment showed no significant differences between the two groups, both by on-treatment and intention-to-treat analysis (Table 4b).

Perioperative outcomes

Perioperative morbidity and mortality were evaluated in the 870 patients who underwent pancreatic resection, after excluding the 76 patients who underwent exploratory or bypass surgery. Of these 870 patients, 16 (1.8%) died. In the 546 patients with resectable tumors, there were no significant differences between the neoadjuvant and surgery-first groups in the proportions that underwent various operative procedures or combined resection of major vessels. Operation time was significantly longer ($P = 0.0001$) and blood loss was significantly greater ($P = 0.0059$) in the neoadjuvant than in the surgery-first group. There were six operative deaths (1.6%) in the surgery-first group and one (0.6%) in the neoadjuvant group ($P = 0.44$). Median postoperative hospital stay was significantly longer

Table 4 Resection and R0-resection rate: (a) Resectable ($n = 582$) and (b) Borderline ($n = 389$)

Group	Surgery first	Neoadjuvant	*P*-value
(a) Resectable ($n = 582$)			
Total cohort, *n*	397	185	–
Resection, *n*	375	171	0.34
Resection rate	94.5%	92.4%	
R0 resection, *n*	305	164	
R0 rate by on-treatment analysis[a]	81.3%	95.9%	<0.0001
R0 rate by intention-to-treat analysis[b]	76.8%	88.6%	0.0003
(b) Borderline ($n = 389$)			
Total cohort	186	203	–
Resection	156	158	
Resection rate	83.9%	77.8%	0.16
R0 resection	118	123	
R0 rate by on-treatment analysis[a]	75.6%	77.8%	0.57
R0 rate by intention-to-treat analysis[b]	63.4%	60.6%	0.61

[a] R0 rate by on-treatment analysis was R0 resection per all resected cases with a record of residual tumor assessment

[b] R0 rate by intention-to-treat analysis was R0 resection per total cases with a record of residual tumor assessment including non-resected and non-operated cases as R2 resection

($P = 0.0020$), and morbidity rate was slightly but not significantly higher ($P = 0.084$) in the neoadjuvant than in the surgery-first group. There were no significant differences in specific postoperative complications, including pancreatic fistula and delayed gastric emptying, as well as in rates of severe complications and reoperation (Table 5).

Of the 314 patients who underwent resection for borderline resectable tumors, those who received neoadjuvant treatment were significantly more likely to undergo resection of the pancreas head ($P = 0.0026$) and portal vein ($P = 0.0018$) than those who underwent surgery first. Operation time was significantly longer in the neoadjuvant than in the surgery-first group ($P = 0.0005$), but there were no between group differences in blood loss ($P = 0.16$), mortality ($P = 0.17$), and hospital stay ($P = 0.50$) (Table 6). Morbidity tended to be less frequent in the neoadjuvant group than in the surgery-first group ($P = 0.057$). In contrast to patients with resectable tumors, the postoperative pancreatic fistula (POPF) rates in patients with borderline resectable tumors were significantly lower in the neoadjuvant group than in the surgery-first group, both for all grades ($P = 0.022$) and grade B/C ($P = 0.015$). Fluid collection was significantly more frequent in the neoadjuvant than in the surgery-first group ($P = 0.016$). Other specific complications and their severity were similar in these two groups (Table 6). In the resectable group with neoadjuvant therapy followed by resection, the proportion of delayed gastric emptying (DGE) in chemoradiotherapy was significantly higher than that in chemotherapy (21.6% vs. 10.1%, $P = 0.0015$). The proportion of other postoperative complications as well as severity of complications and reoperation listed in Table 5 was similar in both treatment modalities. In the borderline group with neoadjuvant therapy followed by resection, the proportion of grade B/C POPF in chemotherapy was slightly, but not statistically significant, higher than that in chemoradiotherapy (10.5% vs. 4.8%, $P = 0.092$). The proportion of other postoperative complications as well as severity of complications and reoperation listed in Table 6 was similar in both treatment modalities.

Histological staging

Table 7 shows a univariate comparison of histological staging according to the American Joint Committee on Cancer (AJCC). Of patients with resectable tumors, those who received neoadjuvant therapy had a lower T grade of the primary tumor than those who underwent surgery first ($P = 0.033$). Moreover, the percentage of patients with lymph node-positive tumors was significantly lower in the neoadjuvant than in the surgery-first group (30.6% vs. 55.2%, $P < 0.0001$), resulting in a significantly lower stage in the former ($P < 0.0001$). In patients with borderline resectable tumors, those who received neoadjuvant treatment had a significantly lower grade of the primary tumor ($P = 0.042$), a significantly lower rate of node-positive tumors (44.3% vs. 74.8%, $P < 0.0001$), and a significantly lower tumor stage ($P < 0.0001$).

Discussion

This survey clarified the feasibility, efficacy, and perioperative outcomes including resectability following

Table 5 Peri-operative outcome in resecteable group

Group	Surgery first	Neoadjuvant	*P*-value
Resection, *n*	375	171	–
PD, *n* (%)	236 (62.9)	111 (64.9)	0.66
DP, *n* (%)	126 (33.6)	52 (30.4)	0.46
TP, *n* (%)	12 (3.2)	7 (4.1)	0.60
PV resection, *n* (%)	71 (18.9)	37 (21.6)	0.46
Arterial resection, *n* (%)	4 (1.1)	4 (2.3)	0.27
Operative time (ml), median (range)	404 (141–829)	470 (157–1,021)	0.0001
Blood loss (ml), median (range)	872 (50–16,422)	1,088 (55–12,925)	0.0059
Blood transfusion (U), median (range)	2 (0–52)	2 (0–16)	0.65
Postoperative hospital stay (day), median (range)	31 (7–167)	36 (8–115)	0.0020
Morbidity, *n* (%)	194 (51.7)	102 (59.7)	0.084
POPF (all grade), *n* (%)	90 (24.0)	35 (20.5)	0.36
POPF (grade B/C), *n* (%)	43 (11.5)	20 (11.7)	0.94
DGE	40 (10.7)	27 (15.8)	0.10
Hemorrhage	16 (4.3)	7 (4.1)	0.93
Abscess	38 (10.1)	19 (11.1)	0.73
Wound infection	30 (8.0)	17 (9.9)	0.46
Leakage[a]	5 (1.3)	6 (3.5)	0.11
Pneumonitis	8 (2.1)	3 (1.8)	>0.99
Thrombosis	3 (0.8)	2 (1.2)	0.65
Cardiac disease	4 (1.0)	0 (0.0)	0.31
Brain	0 (0.0)	1 (0.6)	0.31
Fluid collection/	16 (4.3)	4 (2.3)	0.33
Hepatic disorder	4 (1.1)	4 (2.3)	0.27
Catheter infection	3 (0.8)	2 (1.2)	0.65
Ileus	4 (1.1)	1 (0.6)	>0.99
Cholangitis	4 (1.1)	0 (0.0)	0.31
Diarrhea/enteritis	10 (2.7)	6 (3.5)	0.59
DIC	2 (0.5)	1 (0.6)	>0.99
UTI	1 (0.3)	1 (0.6)	0.53
Renal disorder	2 (0.5)	0 (0.0)	>0.99
Anaphylaxis	1 (0.3)	1 (0.6)	0.53
Sepsis	1 (0.3)	0 (0.0)	>0.99
Splenic infarction	1 (0.3)	1 (0.6)	0.53
Peptic ulcer	1 (0.3)	0 (0.0)	>0.99
Herpes Zoster	2 (0.5)	0 (0.0)	>0.99
Portal vein trouble	1 (0.3)	0 (0.0)	>0.99
Severe complication (Grade IIIa–V), *n* (%)	58 (15.8)	23 (13.9)	0.59
Reoperation	9 (2.4)	7 (4.1)	0.29
Mortality, *n* (%)	6 (1.6)	1 (0.6)	0.44

[a] Leakage includes anastomosis insufficiency except for pancreatic fistula

neoadjuvant therapy in patients with pancreatic cancer. Adjuvant chemotherapy with gemcitabine is a standard therapy following resection for pancreatic cancer and significantly enhances recurrence-free and overall survival compared with surgery alone, with a median overall survival of almost 2 years after surgery [3–5]. However, this approach of surgery followed by adjuvant therapy cannot be offered to a significant proportion of patients with pancreatic cancer because of risks of surgical morbidity and the presence of unresectable disease at laparotomy. In contrast, almost all patients can receive neoadjuvant therapy before surgery [17, 18].

A major concern in treating these patients with neoadjuvant therapy is the risks of operative morbidity and

Table 6 Peri-operative outcome in borderline group

Group	Surgery first	Neoadjuvant	*P*-value
Resection, *n*	156	158	–
PD, *n* (%)	95 (60.9)	121 (76.6)	0.0026
DP, *n* (%)	51 (32.7)	31 (19.6)	0.0081
TP, *n* (%)	9 (5.8)	6 (3.8)	0.44
PV resection, *n* (%)	84 (53.9)	112 (70.9)	0.0018
Arterial resection, *n* (%)	13 (8.3)	10 (6.3)	0.50
Operative time (ml), median (range)	496 (161–1,221)	567 (190–1,160)	0.0005
Blood loss (ml), median (range)	1,137 (20–16,201)	1,400 (60–8,422)	0.16
Blood transfusion (U), median (range)	4 (0–54)	4 (0–18)	0.51
Postoperative hospital stay (day), median (range)	30 (7–397)	31 (8–124)	0.50
Morbidity, *n* (%)	93 (50.0)	82 (40.4)	0.057
POPF (all grade), *n* (%)	34 (18.3)	16 (7.9)	0.0022
POPF (gradeB/C), *n* (%)	19 (10.2)	8 (3.9)	0.015
DGE	24 (12.9)	20 (9.9)	0.34
Hemorrhage	3 (1.6)	4 (2.0)	0.55
Abscess	16 (8.6)	17 (6.4)	0.41
Wound infection	18 (9.7)	20 (9.9)	0.95
Leak[a]	8 (4.3)	3 (1.5)	0.13
Pneumonitis	2 (1.1)	4 (2.0)	0.69
Thrombosis	1 (0.5)	1 (0.5)	1.0
Cardiac disease	0 (0.0)	2 (1.0)	0.50
Brain	2 (1.1)	1 (0.5)	0.61
Fluid collection/	5 (2.7)	17 (8.4)	0.016
Hepatic disorder	3 (1.6)	5 (2.5)	0.73
Catheter infection	1 (0.5)	2 (1.0)	0.53
Ileus	1 (0.5)	0 (0.0)	0.48
Cholangitis	2 (1.1)	2 (1.0)	0.65
Diarrhea/enteritis	4 (2.2)	9 (4.4)	0.26
DIC	0 (0.0)	0 (0.0)	–
UTI	0 (0.0)	0 (0.0)	–
Renal disorder	0 (0.0)	0 (0.0)	–
Anaphylaxis	0 (0.0)	0 (0.0)	–
Splenic infarction	0 (0.0)	0 (0.0)	–
Peptic ulcer	1 (0.5)	1 (0.5)	1.0
Herpes Zoster	0 (0.0)	0 (0.0)	–
Portal vein trouble	1 (0.5)	1 (0.5)	1.0
Severe complication (Grade IIIa–V), *n* (%)	22 (14.5)	21 (13.7)	0.85
Reoperation	6 (3.9)	6 (3.8)	0.98
Mortality, *n* (%)	2 (1.3)	7 (4.4)	0.17

[a] Leakage includes anastomosis insufficiency except for pancreatic fistula

mortality. Although several small prospective studies have demonstrated the feasibility of this approach [10, 11, 19], this has not been confirmed because of the small sample sizes. Several nationwide surveys [20, 21] and systematic reviews and meta-analyses [22, 23] indicated that this strategy was feasible in larger numbers of patients, but could not quantify the data. Only one systematic review showed the rate of surgical morbidity and mortality after neoadjuvant therapy [24]. We found that neoadjuvant treatment did not significantly increase perioperative mortality and morbidity rates, including pancreatic fistula and delayed gastric emptying, indicating that neoadjuvant treatment was a feasible strategy in patients with pancreatic cancer. Neoadjuvant therapy, however, resulted in significantly longer operation times and postoperative hospital stay, as well as higher rates of grade 3/4 hematological toxicities. Nevertheless, these preoperative toxicities were manageable, with <0.5% of patients becoming ineligible for surgery.

Table 7 Peri-operative outcome in resecteable group: (a) Resectable and (b) Borderline

		Surgery first	Neoadjuvant	*P*-value
(a) Resectable				
T	0	1 (0.3)	2 (1.2)	0.033
	1	33 (8.8)	28 (16.5)	
	2	35 (9.3)	13 (7.7)	
	3	304 (81.1)	124 (72.9)	
	4	2 (0.5)	3 (1.8)	
N	0	168 (44.8)	118 (69.4)	<0.0001
	1	207 (55.2)	52 (30.6)	
M	0	354 (94.4)	160 (94.1)	0.895
	1	21 (5.6)	10 (5.9)	
Stage	0	0 (0)	2 (0.4)	<0.0001
	IA	28 (7.5)	24 (14.1)	
	IB	28 (7.5)	10 (5.9)	
	IIA	110 (29.3)	81 (47.7)	
	IIB	186 (49.6)	40 (23.5)	
	III	2 (0.5)	3 (1.7)	
	IV	21 (5.6)	10 (5.9)	
(b) Borderline				
T	0	2 (1.3)	1 (0.6)	0.042
	1	2 (1.3)	12 (7.6)	
	2	4 (2.6)	9 (5.7)	
	3	140 (90.3)	129 (82.2)	
	4	7 (4.5)	6 (3.8)	
N	0	39 (25.2)	88 (55.7)	<0.0001
	1	116 (74.8)	70 (44.3)	
M	0	132 (85.2)	143 (90.5)	0.895
	1	23 (14.8)	15 (9.5)	
Stage	0	0 (0.0)	1 (0.6)	<0.0001
	IA	1 (0.7)	10 (6.3)	
	IB	2 (1.3)	5 (3.2)	
	IIA	32 (20.7)	64 (40.5)	
	IIB	91 (58.7)	58 (36.7)	
	III	6 (3.9)	5 (3.2)	
	IV	23 (14.8)	15 (9.5)	

Another concern associated with the neoadjuvant strategy is a possible decrease in tumor resectability due to tumor progression during preoperative treatment. A meta-analysis showed that, of patients with resectable tumors, 73.6% to 82.9% remained resectable after neoadjuvant therapy [17, 24], findings similar to those in patients scheduled for primary resection and adjuvant therapy. We found that neoadjuvant therapy did not decrease tumor resectability, both in patients with resectable and borderline resectable pancreatic cancers. Intention-to-treat analysis showed that, in resectable tumors, the curability (R0 resection rate) was improved after neoadjuvant treatment. Radiologically, 90% of patients who received neoadjuvant therapy showed lack of tumor progression or tumor shrinkage, with only 10% showing tumor progression, suggesting that neoadjuvant treatment increased the likelihood of curative resection. These advantages of neoadjuvant therapy, however, were not observed in patients with borderline resectable disease, and resectability and R0 resectability were similar in the neoadjuvant and surgery-first groups. The incidence of nodal involvement was significantly lower in the neoadjuvant than in the surgery-first group. Neoadjuvant therapy has been reported to reduce the number of lymph node metastases [25, 26], suggesting that the main effect of neoadjuvant therapy is to reduce peripancreatic lymph node positivity rather than the size of primary tumors. Since nodal involvement is one of the most significant predictors of patient survival [27, 28], neoadjuvant therapy may have a survival benefit following resection of pancreatic cancer.

Although the number of patients receiving neoadjuvant therapy is the largest to date, questionnaire surveys have limitations. Data were collected from the various treatment centers retrospectively, not prospectively. In addition, there was significant inter-center heterogeneity in eligibility criteria for neoadjuvant treatment, neoadjuvant regimens, radiologic and intraoperative indications for resection, and postoperative therapy regimens. This heterogeneity may have introduced selection biases, preventing definite conclusions. Prospectively designed trials with adequate numbers of patients are required to determine the feasibility and efficacy of neoadjuvant treatment in patients with pancreatic cancer. This survey analyzing the effects of neoadjuvant treatment on resectablity and perioperative outcomes in patients with pancreatic cancer could not determine the impact of treatment on survival. However, several studies have reported that neoadjuvant therapy had survival benefits in patients with resectable or borderline resectable pancreatic cancer [11, 17, 21, 22, 24]. These suggest the need for prospective randomized studies to clarify the effects on survival of neoadjuvant therapy compared with the standard surgery-first strategy, in patients with pancreatic cancer [12, 18]. In conclusion neoadjuvant therapy may not increase the mortality and morbidity rates, and may be able to increase the chance for curative resection especially against resectable tumor.

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ORIGINAL ARTICLE

Indication for the use of an interposed graft during portal vein and/or superior mesenteric vein reconstruction in pancreatic resection based on perioperative outcomes

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Abstract
Purpose Combined portal vein and/or superior mesenteric vein (PV/SMV) resection with pancreatic resection sometimes leads to prolonged survival for patients with pancreatic cancer. In this study, we evaluated perioperative outcomes of patients with PV/SMV reconstruction and considered indications for the use of a graft during this procedure.
Methods We performed PV/SMV resection with pancreatic resection in 128 patients, including 14 using grafts. Complications associated with PV/SMV reconstruction and harvesting venous grafts and reconstructed PV/SMV patency during follow-up were assessed.
Results Of the 128 patients, 5 underwent total pancreatectomy, 99 pancreaticoduodenectomy, and 24 distal pancreatectomy. In the 14 patients who underwent PV/SMV reconstruction with grafts, the grafts were harvested from the external iliac vein (EIV) in 10 patients and internal jugular vein (IJV) in the other 4. Five patients (3.9 %) had an intraoperative or postoperative acute thrombus or stenosis of reconstructed PV/SMV after direct end-to-end anastomosis. However, PV/SMV patency was excellent after reconstruction using grafts. There were no significant differences in other complications between groups with and without the use of grafts. Three patients (30 %) with EIV grafts had postoperative leg edema, and one of them required analgesics until his death because of leg pain caused by compartment syndrome, whereas no patients with IJV grafts had complications associated with sacrificing veins.
Conclusions Depending on the length and/or position of the removed PV/SMV segment, interposed graft may be required for reconstruction in some patients, and the use of graft vein, particularly using IJV, is an appropriate procedure that is not associated with any complications.

Keywords Portal vein reconstruction using a graft · Pancreatectomy · External iliac vein graft · Internal jugular vein graft · Portal vein thrombus

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Introduction

Pancreatic resection with combined portal vein and/or superior mesenteric vein (PV/SMV) resection is sometimes required for macroscopic complete resection (R0/R1) of pancreatic cancer. Until the early 1990s, the PV/SMV resection was generally considered to be contraindicated [1–3], because of its high morbidity and mortality. However, as surgical techniques have progressed, the morbidity and mortality rates have been reduced to acceptable levels [4–7]. The techniques used for PV/SMV resection and reconstruction are mainly classified into three types: (1) primary tangential resection and venorrhaphy; (2) primary circumferential resection and end-to-end anastomosis; and (3) primary circumferential resection and anastomosis with graft interposition. In most patients, PV/SMV reconstruction can be performed by direct suturing or direct end-to-end anastomosis between the resected PV and SMV without any interposed grafts during pancreatic resection [4–8]. However, when a direct end-to-end anastomosis has a risk of stenosis or over-tension of the reconstructed PV/SMV, an interposed graft will be necessary [1], because the development of a postoperative acute PV/SMV thrombus leads to bowel ischemia, sepsis, and death. It

remains unclear which patients are indicated for the use of an interposed graft for PV/SMV reconstruction in pancreatic resection to prevent postoperative PV/SMV thrombus.

The PV has a large diameter for low pressure but high volume flow. The usefulness of polytetrafluoroethylene graft as an artificial graft has been reported [9, 10], and the left renal vein [11–13], external iliac vein (EIV) [6, 14, 15], internal jugular vein (IJV) [1], femoral vein [16], and customized gonadal vein [17] or saphenous vein [18] can be used as an autologous vein graft. However, the most appropriate graft for PV/SMV reconstruction in pancreatic resection remains controversial.

In this report, we review 128 patients who underwent combined PV/SMV resection during pancreatic resection. The aims of the present study were to analyze the perioperative complications associated with PV/SMV reconstruction and venous graft harvesting and to consider which patients should be treated using an interposed graft and what kind of graft is available for PV/SMV reconstruction.

Materials and methods

Patients

Between January 2000 and December 2012, 766 consecutive patients underwent pancreatic resection at the Wakayama Medical University Hospital (WMUH); among them, 128 patients underwent a combined resection of the PV/SMV. The records of these patients were retrospectively reviewed. This retrospective study was approved by the Human Ethics Review Committee of WMUH. The characteristics of the patients are summarized in Table 1.

Surgical procedures

The patients with pancreatic head cancer received pancreatoduodenectomy (PD) with lymphatic dissection around the pancreatic head, right gastroepiploic artery, common hepatic artery, proper hepatic artery, and superior mesenteric artery (SMA), and right semicircle nerve plexus of SMA dissection, as a standard operation. The patients with pancreatic body cancer received distal pancreatectomy (DP) with lymphatic dissection around pancreatic body and tail, spleen, common hepatic artery, splenic artery, left gastric artery, celiac artery, middle colic artery, and SMA, and left semicircle nerve plexus of SMA dissection, as a standard operation. If the nerve plexus invasion of the celiac artery was suspected, we performed DP with celiac axis resection (DP-CAR).

Regarding the criteria for selecting either a tangential or circumferential resection of the PV/SMV, if tumor involvement of less than one-quarter of the PV/SMV wall was suspected, a tangential PV/SMV resection was chosen; otherwise, circumferential resection was chosen when venous involvement appeared to be more extensive. Mobilization of the right hemicolon (ascending colon and half of transverse colon) was performed for PV/SMV tension-free anastomosis with carefully avoiding the twist of intestinal root and reconstructed PV/SMV. If the combined PV/SMV resection was considered to be in over-tension or stenosis of the primary anastomosis, reconstruction with an autologous venous graft was chosen. We used the EIV or IJV as an autologous graft for PV/SMV reconstruction. Before the operation, all patients provided their informed consent to have an EIV or IJV resected for an autologous venous graft, if it was required for PV/SMV reconstruction.

During PV/SMV reconstruction with an autologous venous graft, we harvested the EIV or IJV, and each stump of the resected EIV or IJV was closed with continuous sutures using 5–0 polypropylene. The harvested graft was interposed into the PV/SMV defect and anastomosed with 6–0 polypropylene sutures using a running technique (intraluminal suturing of the posterior wall and over-and-over suturing to the anterior wall). The SMA was routinely clamped during reconstruction to avoid intestinal venous congestion. Doppler signals in the graft were assessed to evaluate the flow intraoperatively.

Postoperative complications and graft surveillance

The postoperative complications and reconstructed PV/SMV patency and blood flow were assessed. We performed postoperative Doppler ultrasonography on postoperative days (POD) 1–3 and enhanced computed tomography (CT) on POD4 to evaluate the PV/SMV flow and patency in all patients with PV/SMV reconstruction. Pancreatic fistula was defined according to the International Study Group of Pancreatic Fistula (ISGPF) guidelines [19], and ISGPF grade B and C were included as postoperative complications in this study. Delayed gastric emptying (DGE) was defined according to the consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS) [20]. DGE was classified into three categories (grade A, B, or C) by the ISGPS clinical criteria based on the clinical course and postoperative management of the patients. Other postoperative complications were graded according to the Clavien classification [21], and the complications in this study were defined as those that were more than grade II. All patients were followed up until death or last follow-up, and the mean duration of follow-up was 28.2 months (range 0.2 to 179 months).

Statistical analysis

We compared the perioperative outcomes between the patients undergoing pancreatic resection with and without combined PV/SMV reconstruction and between those undergoing PV/

Table 1 Comparison of the patients undergoing pancreatectomy without and with combined portal vein and/or superior mesenteric vein (PV/SMV) resection

	All patients with pancreatectomy			Pancreatic cancer patients with pancreatectomy		
	With PV/SMV resection (n=128)	Without PV/SMV resection (n=638)	P	With PV/SMV resection (n=119)	Without PV/SMV resection (n=263)	P
Gender (male/female)	72/56	364/274	0.867	67/52	149/114	0.949
Median age, years (range)	67 (41–86)	70 (18–91)	0.017	67 (41–86)	70 (31–91)	0.012
Final pathological diagnosis, n (%)			<0.001			–
Pancreatic cancer	119 (93.0)	263 (41.2)		119	263	
Bile duct cancer	6 (4.7)	142 (22.3)		0	0	
IPMN	0 (0)	122 (19.1)		0	0	
Tumor-forming pancreatitis	1 (0.8)	31 (4.9)		0	0	
Neuroendocrine tumor	0 (0)	26 (4.1)		0	0	
Duodenal cancer	0 (0)	15 (2.4)		0	0	
Serous cystic neoplasm	1 (0.8)	8 (1.3)		0	0	
Mucinous cystic neoplasm	0 (0)	8 (1.3)		0	0	
Solid-pseudopapillary neoplasm	1 (0.8)	2 (0.3)		0	0	
Others	0 (0)	21 (3.3)		0	0	
Surgical procedure, n (%)			<0.001			<0.001
Total pancreatectomy	5 (3.9)	32 (5.0)		5 (4.2)	19 (7.2)	
Pancreaticoduodenectomy	99 (77.3)	434 (68.0)		91 (76.5)	142 (54.0)	
Pancreaticoduodenectomy	18	68		16	25	
Pylorus-preserving pancreaticoduodenectomy	21	140		18	43	
Pylorus-resecting pancreaticoduodenectomy	60	226		57	74	
Distal pancreatectomy	12 (9.4)	148 (23.2)		11 (9.2)	78 (29.7)	
Distal pancreatectomy with celiac axis resection	12 (9.4)	24 (3.8)		12 (10.1)	24 (9.1)	
Combined resection, n (%)	24 (18.8)	70 (11.0)	0.014	23 (19.3)	36 (13.7)	0.158
Stomach	8	20		8	10	
Colon	6	18		5	11	
Adrenal gland	12	19		12	11	
Liver	1	12		1	0	
Kidney	1	5		1	2	
Others	2	9		0	4	
Median operative time, min (range)	456 (235–958)	337.5 (40–661)	<0.001	455 (235–958)	328 (120–633)	<0.001
Median surgical blood loss, ml (range)	1,045 (30–13,300)	549 (10–6,320)	<0.001	1,030 (30–13,300)	567.5 (20–6,320)	<0.001
Intraoperative red blood cell transfusion, n (%)	67 (52.3)	160 (25.1)	<0.001	61 (51.3)	69 (26.2)	<0.001
Surgical morbidity, n (%)	38 (29.7)	179 (28.1)	0.709	32 (26.9)	65 (24.7)	0.651
Portal vein thrombosis	2 (1.6)	1 (0.2)	0.020	1 (0.8)	0 (0)	0.137
Leg edema	3 (2.3)	0 (0)	<0.001	2 (1.7)	0 (0)	0.035
Pancreatic fistula (Grade B/C)*	18 (14.1) (6/2)	82 (12.9) (65/17)	0.711	16 (13.4) (14/2)	25 (9.5) (17/8)	0.250
Delayed gastric empty (Grade A/B/C)**	12 (9.4) (3//6/3)	66 (10.3) (27/26/13)	0.741	12 (10.1) (3/6/3)	27 (10.3) (12/9/6)	0.957
Hemorrhage (abdominal/digestive bleeding)	7 (5.5) (4/3)	24 (3.8)	0.371	6 (5.0) (4/2)	10 (3.8) (9/1)	0.576
Abdominal abscess	12 (9.4)	37 (5.8)	0.132	10 (8.4)	11 (4.2)	0.094
Pulmonary complication	6 (4.7)	9 (1.4)	0.015	5 (4.2)	3 (1.1)	0.053
Mortality (in hospital)	6 (4.7)	10 (1.6)	0.024	4 (3.4)	4 (1.5)	0.245
Median hospital stay, days (range)	21 (8–190)	20 (5–740)	0.042	19 (8–190)	18 (6–194)	0.031

*Pancreatic fistula was defined according to the International Study Group of Pancreatic Surgeons

**Delayed gastric emptying was defined according to the International Study Group of Pancreatic Surgeons

SMV reconstruction with and without an autologous vein graft. The associations between categorical and continuous variables were assessed by the chi-square test (or Fisher's exact test, as appropriate) and the Mann-Whitney U test, respectively. Regarding surgical margin, R0 was defined as no microscopic evidence of cancer cells at all surgical

margins, R1 as the microscopic presence of cancer cells at surgical margins, and R2 as the macroscopic presence of cancer found during surgery. Overall survival (OS) was measured from surgery resection until death or the last follow-up and estimated using the Kaplan-Meier method, and differences were assessed by the log-rank test. Differences were considered to be significant when $P<0.05$. All analyses were performed using the SPSS version 20.0 software program for Microsoft Windows (SPSS, Inc. Chicago, IL).

Results

Comparison of perioperative outcomes between pancreatic resection with and without PV/SMV resection

Regarding surgical procedure, PD was more often performed in the PV/SMV resection group than in the group without PV/SMV resection (Table 1). The operative time and the blood loss were greater in the PV/SMV resection group (median operative time 456 vs. 337.5 min, $P<0.001$; median blood loss 1,045 vs. 549 ml, $P<0.001$). The mortality of the PV/SMV resection group was higher, although there was no difference in morbidity between the two groups (Table 1). However, in 382 patients with pancreatic cancer who underwent lymphatic dissection, there were no differences in morbidity and mortality between pancreatectomy with and without PV/SMV resection (Table 1).

Pancreatic resection with combined PV/SMV resection and reconstruction

We performed combined PV/SMV resection and reconstruction with pancreatic resection in 128 patients. Among them, 5 patients (3.9 %) underwent total pancreatectomy, 99 (77.3 %) underwent PD, 12 (9.4 %) underwent DP, and 12 (9.4 %) underwent DP-CAR. Only PV resection was performed in 15 patients (11.7 %), only SMV resection in 42 patients (32.8 %), and combined PV and SMV resection in 71 patients (55.5 %).

Among the 128 patients with combined PV/SMV resection in the pancreatic resection, 11 (8.6 %) had a tangential resection of the PV/SMV, 103 (80.5 %) had a circumferential resection and primary end-to-end anastomosis of the PV/SMV, and 14 (10.9 %) had a circumferential resection of the PV/SMV and reconstruction with an autologous graft.

PV/SMV reconstruction with an autologous vein graft

The details of the 14 patients who underwent PV/SMV reconstruction with the use of an autologous vein graft are shown in Table 2. Eleven of the patients with an autologous vein graft were preoperatively and intraoperatively recognized to need a graft, because over-tension of the PV/SMV anastomosis without a graft was expected. The other three patients required conversion from primary direct suturing or end-to-end anastomosis to anastomosis using a graft due to stenosis or over-tension. One patient (case 2 in Table 2) had a tumor located in the uncinate process; he underwent PD with a combined 5-cm SMV resection and primary end-to-end anastomosis at the jejunal and iliac branch junction of the SMV and was found to have SMV thrombus at the primary anastomosis during the operation (Fig. 1a). The other patients, whose tumors were located in the pancreatic body and had strong adherence to the PV and SMV confluence, underwent DP with combined PV and SMV confluent resection. One of these patients (case 10) was found to have PV/SMV stenosis after direct suturing of the defect (Fig. 1b), and the other (case 13) was found to have a thrombus in the PV/SMV after the primary end-to-end anastomosis during the operation (Fig. 1c).

The grafts were harvested from a right EIV in 10 patients and a right IJV in 4 patients. The mean graft length of the EIV or IJV obtained was 3.7 cm (range 2.0–5.0 cm).

Complications associated with the harvest of an autologous vein graft

Three of 10 patients (30 %) who underwent harvesting of a graft from the EIV were found to have obvious edema of the ipsilateral leg caused by acute deep vein thrombus extending downward from the distal ligated edge of the EIV on POD1. They underwent therapeutic anticoagulation with intravenous heparin for 7 days (POD1–7) and then received an oral drug (with anti-vitamin K) for anticoagulation. As a result, their ipsilateral leg edema was relieved within 3 weeks in all three cases. However, one patient (case 10 in Table 2) was troubled by pain of the dorsum pedis while walking until he died of cancer 2 years later. Based on this case, we decided to change from using the EIV to the IJV as the PV/SMV graft. All four patients whose grafts were harvested from their right IJV had no venous insufficiency and no complications involving the head and neck.

General perioperative outcomes in the patients with combined PV/SMV resection in pancreatic resection

We compared the operative outcomes between PV/SMV reconstruction with and without the use of a graft. There were no statistically significant differences in the patient age, gender, type of surgical procedure, and frequency of intraoperative transfusion rates between the patients who underwent PV/SMV reconstruction with and without a graft. The operative time and the blood loss in PV/SMV reconstruction with a graft were greater than those without a graft (median operative time 572.5 vs. 450 min, $P<0.001$; median blood loss 2,387 vs. 987.5 ml, $P=0.001$). The length of the

Table 2 Characteristics and intraoperative outcomes of patients who underwent portal vein and/or superior mesenteric vein reconstruction with an autologous graft

Patient No.	Age (years)/ gender	Disease (tumor size)	Surgical procedures	Graft	Operative time (min)	Blood loss (mL)	Length of resected PV/ harvested graft vein	Clamping time (min)	Intraoperative complications	Postoperative complications
1.	67/M	Pancreatic cancer (3 cm)	PD, PV-SMV resection	EIV	560	1,570	5 cm/3 cm	27	none	none
2.	41/M	Pancreatic cancer (4.5 cm)	PD, PV-SMV resection	EIV	610	4,940	5 cm/2 cm	36	PV/SMV thrombosis after primary end-to-end anastomosis	abdominal abscess, paralytic ileus
3.	71/F	Pancreatic cancer (3 cm)	PpPD, PV-SMV resection	EIV	559	2,435	4 cm/4 cm	26	none	none
4.	70/M	Pancreatic cancer (3 cm)	PD, PV-SMV resection	EIV	585	10,080	5 cm/3 cm	27	none	pneumonia, digestive bleeding
5.	54/M	Pancreatic cancer (3.5 cm)	PrPD, SMV resection	EIV	518	305	4 cm/3 cm	26	none	none
6.	65/F	Pancreatic cancer (3.5 cm)	PrPD, SMV resection	EIV	519	2,340	6 cm/5 cm	25	none	none
7.	77/M	Pancreatic cancer (8 cm)	PrPD, PV resection	EIV	651	3,510	5 cm/5 cm	26	none	right leg edema
8.	61/F	Serous cyst neoplasm (16 cm)	PrPD, PV-SMV resection	EIV	459	8,090	8,090 5 cm/5 cm	25	none	right leg edema
9.	75/M	Pancreatic cancer (8 cm)	TP, PV-SMV resection	EIV	544	5,790	4 cm/3 cm	27	none	none
10.	51/M	Pancreatic cancer (3 cm)	DP, Partial gastrectomy, PV-SMV resection	EIV	413	1,075	3 cm/3 cm	25	PV/SMV stenosis after primary direct suturing of the PV/SMV defect	right leg edema with pain
11.	68/M	Pancreatic cancer (3.5 cm)	PrPD, PV-SMV resection	IJV	620	1,115	5 cm/3 cm	39	none	none
12.	76/M	Pancreatic cancer (7.8 cm)	DP-CAR, PV-SMV resection	IJV	686	9,900	7 cm/5 cm	26	none	pancreatic fistula (grade C) abdominal bleeding
13.	52/M	Solid-pseudopapillary neoplasm (12 cm)	DP, Right colectomy PV-SMV resection	IJV	706	2,005	4 cm/3 cm	43	PV/SMV thrombosis after primary end-to-end anastomosis	none
14.	68/M	Pancreatic cancer (4.0 cm)	PrPD, PV-SMV resection	IJV	429	429 460	6 cm/5 cm	29	none	none

PD Pancreaticoduodenectomy, *PV* portal vein, *SMV* superior mesenteric vein, *EIV* external iliac vein, *IJV* internal jugular vein, *PpPD* pylorus-preserving pancreaticoduodenectomy, *PrPD* pylorus-resecting pancreaticoduodenectomy, *TP* total pancreatectomy, *DP* distal pancreatectomy, *DP-CAR* distal pancreatectomy with celiac axis resection

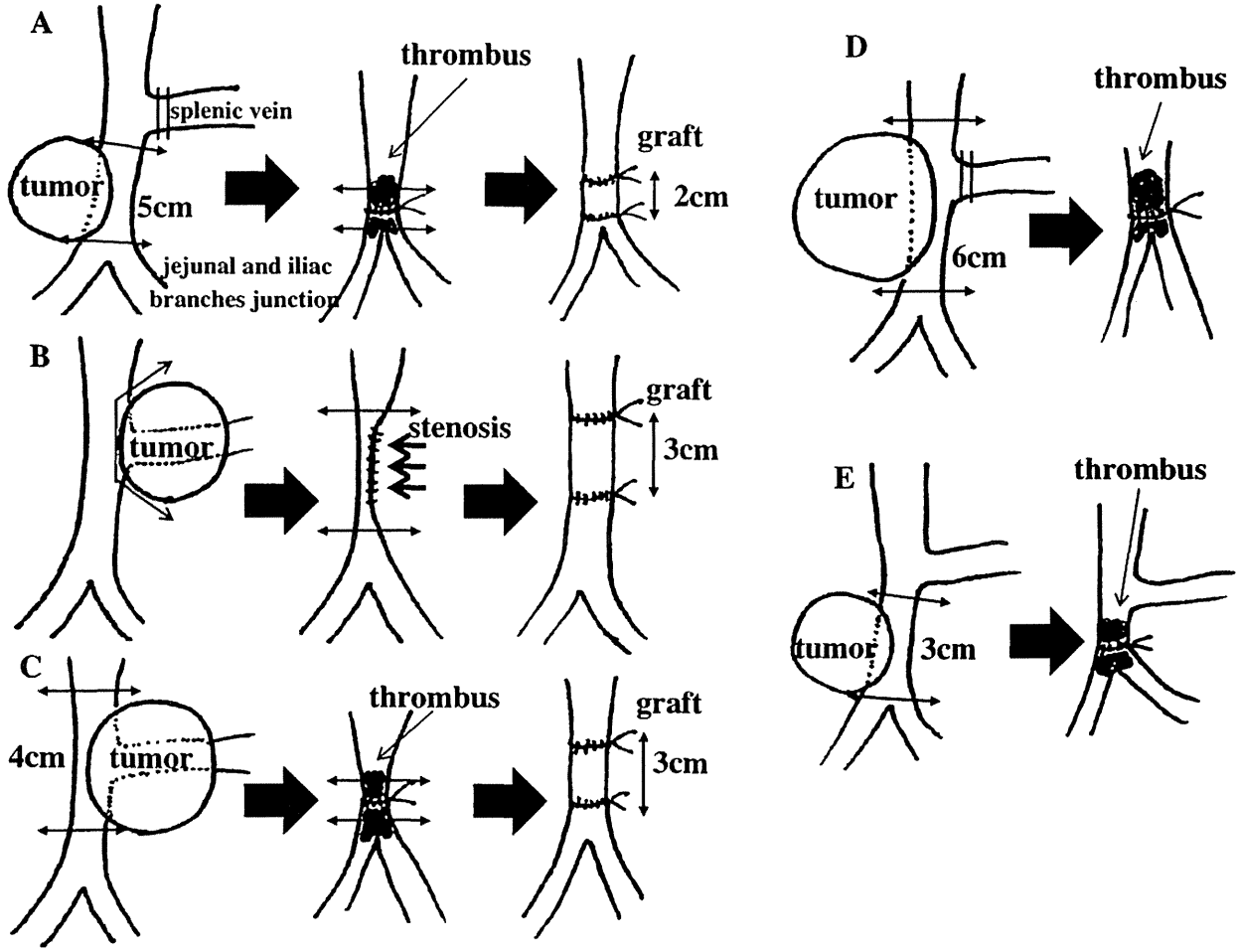

Fig. 1 Three patients required revision of the portal vein and/or superior mesenteric vein (PV/SMV) reconstruction using an interposed graft during their operation (a–c). Two patients were found to have a postoperative acute thrombus in the reconstructed PV/SMV (e, f) and required site-directed venous thrombolytic therapy

resected PV/SMV segment and the SMA and PV/SMV clamping time during PV/SMV reconstruction in patients with a graft were longer than those without a graft (median length 5.0 vs. 2.0 cm, $P<0.001$; median clamping time 26 vs. 15 min, $P<0.001$; Table 3).

There were no statistically significant differences in the mortality and morbidity between the groups. Two patients with PV/SMV reconstruction with a graft died during their hospital stay: one patient died of pneumonia on POD68, and the other died of abdominal hemorrhage on POD49. Four patients (3.7 %) with PV/SMV reconstruction without a graft died during their hospital stay: one of them died of pneumonia on POD8; 2 patients died of hemorrhage on POD18 and POD28, respectively; and the other patient died of liver failure on POD52. There was no difference in the length of the hospital stay between the patients with and without a graft (Table 3).

Complications associated with PV/SMV resection and surveillance of the reconstructed PV/SMV patency

Postoperative thrombus was found in two patients with combined PV/SMV resection and reconstruction with direct primary end-to-end anastomosis without a graft, whereas no patient was found to have PV/SMV thrombus after reconstruction with a graft (Table 3). In one of the patients with thrombus, who underwent a 6-cm resection of both the PV and SMV and primary PV/SMV end-to-end anastomosis (Fig. 1d), the serum aspartate aminotransferase and alanine aminotransferase levels increased on POD9. The patient underwent venography due to an acute PV/SMV thrombus, and a completely occluded PV/SMV caused by an acute thrombus was found. A stent was immediately inserted into the occluded PV/SMV, and recanalization of the PV/SMV through the stent was confirmed. SMA-directed thrombolytic therapy was then

Table 3 Comparison of the patients undergoing pancreatectomy with combined portal vein and/or superior mesenteric vein reconstruction with and without a graft

	With a graft (n=14)	Without a graft (n=114)	P
Gender (Male/Female)	11/3	61/53	0.074
Median age, years (range)	67.5 (41–77)	66.5 (43–86)	0.544
Surgical procedure			0.806
Total pancreatectomy	1 (7.1)	4 (3.5)	
Pancreaticoduodenectomy	10 (71.4)	89 (78.1)	
Pancreaticoduodenectomy	3	15	
Pylorus-preserving pancreaticoduodenectomy	1	20	
Pylorus-resecting pancreaticoduodenectomy	6	54	
Distal pancreatectomy	2 (14.3)	10 (8.8)	
Distal pancreatectomy with celiac axis resection	1 (7.1)	11 (9.7)	
Median operative time, min (range)	572.5 (413–706)	450 (235–958)	<0.001
Median surgical blood loss, ml (range)	2,387 (305–10,080)	987.5 (30–13,330)	0.001
Intraoperative red blood cell transfusion, n (%)	10 (71.4)	57 (50)	0.131
Median length of resected PV/SMV, cm (range)	5.0 (3.0-7.0)	2.0 (0.5-6.0)	<0.001
Median clamping time during reconstruction, min (range)	26 (25–43)	15 (5–30)	<0.001
Surgical morbidity, n (%)	6 (42.9)	31 (27.2)	0.224
Portal vein and/or superior mesenteric vein thrombosis	0 (0)	2 (1.8)	0.619
Leg edema	3 (21.4)	0 (0)	<0.001
Pancreatic fistula (Grade B/C)*	1 (7.1) (0/1)	17 (6.1) (15/2)	0.432
Delayed gastric empty (Grade A/ B/C)**	1 (7.1) (0/0/1)	10 (8.8) (3/6/1)	0.838
Hemorrhage	2 (14.3)	5 (4.4)	0.126
Abdominal/ digestive bleeding	1/1	3/2	
Abdominal abscess	2 (14.3)	10 (8.8)	0.506
Pulmonary complication	1 (7.1)	5 (4.4)	0.646
Mortality (in hospital)	2 (14.3)	4 (3.5)	0.073
Median hospital stay, days (range)	26.5 (14–68)	14 (8–190)	0.054

*Pancreatic fistula was defined according to the International Study Group of Pancreatic Surgeons

**Delayed gastric emptying was defined according to the International Study Group of Pancreatic Surgeons

performed for 7 days until the thrombus disappeared on venography. However, the patient eventually died of liver failure on POD52. Another patient, who underwent a 3-cm resection of the SMV and primary end-to-end anastomosis of the SMV (Fig. 1e), had a clinically silent thrombus found by enhanced CT on POD4. The patient underwent a site-directed thrombolytic therapy for 7 days until we confirmed that the thrombus of the SMV had disappeared by enhanced CT. An oral anticoagulation drug (anti-vitamin K) was then administered to prevent the propagation of the thrombus with its associated bowel ischemia and sepsis. The patient is still alive with no evidence of PV/SMV thrombus.

During the follow-up period, there were no thrombi or occlusion of the PV/SMV anastomosis and grafts, except for four patients whose PV/SMV were occluded due to the local recurrence of pancreatic cancer (POD138, 166, 219, and 415).

Histopathologic findings and survival in the patients with pancreatic ductal adenocarcinoma

The histopathologic findings and OS for 305 patients with pancreatic ductal adenocarcinoma, except for 77 patients with pancreatic cancer derived from intraductal papillary mucinous neoplasm (n=68), acinar cells (n=5), or others (n=4), were evaluated (Table 4). There were no significant differences in TNM stage, R0 rates, and OS between the patients with and without PV/SMV resection (P=0.108, P=0.128, and P=0.354, respectively; Table 4, Fig. 2a), although the lymph node metastasis rates in the patients with PV/SMV resection were higher than those without PV/SMV resection (78.8 vs. 64.6 %, P=0.012). The tumor size in the patients undergoing PV/SMV reconstruction with the use of a graft was larger than that without a graft (mean size 40.5 vs. 29.3 mm, P=0.047), and the R0 rates and OS were not

Table 4 Comparison of histopathological findings and overall survival between pancreatic ductal adenocarcinoma patients undergoing surgical resection with and without portal vein and/or superior mesenteric vein (PV/SMV) reconstruction

	Pancreatic ductal adenocarcinoma patients undergoing surgical resection				
	With PV/SMV reconstruction (n=99)		Without PV/SMV reconstruction (n=206)		P
	n	%	n	%	
Histological positive PV invasion	57	57.6	–	–	–
Surgical margin					0.128
Negative (R0)	70	70.7	162	78.6	
Positive (R1/R2)	29 (29/0)	29.3	44 (39/5)	21.4	
UICC T stage					0.142
T1	1	1.0	8	3.9	
T2	0	0	5	2.4	
T3	92	92.9	186	90.3	
T4	6	6.1	7	3.4	
Positive lymph node metastasis	78	78.8	133	64.6	0.012
UICC stage					1.108
Stage IA	1	1.0	8	3.9	
Stage IB	0	0	3	1.5	
Stage IIA	20	20.2	61	29.6	
Stage IIB	64	64.7	115	55.8	
Stage III	6	6.1	5	2.4	
Stage IV	8	8.1	14	6.8	
Median overall survival (months)	16.6		21.3		0.354
1-year survival (%)	64.8		71.0		
3-year survival (%)	25.5		28.9		
5-year survival (%)	22.3		20.5		

different between the patients with and without a graft (R0 rates 50 vs. 73 %, P=0.129; median OS 23.4 vs. 16.6 months, P=0.323; Fig. 2b).

Discussion

Recent reports have suggested that pancreatic resection with combined PV/SMV resection could prolong the survival in selected patients with malignancy [4, 6, 22, 23], which has lead to increased experiences with this aggressive procedure in high volume centers. In the present study, we found no difference in morbidity and mortality between pancreatic cancer patients undergoing pancreatic resection with or without PV/SMV resection, indicating that PV/SMV resection in pancreatic resection might be a feasible procedure. Furthermore, the R0 rates and OS were not significantly different between pancreatic ductal adenocarcinoma patients with and without PV/SMV resection, despite a more advanced cancer in patients requiring PV/SMV resection in the present study.

The most important aspect of PV/SMV reconstruction is to prevent over-tension or twisting of the reconstructed vessel, because this can lead to acute PV/SMV thrombus formation, which is associated with bowel ischemia, sepsis, and surgical death. The methods used to increase the mobility of the PV/SMV in patients with combined PD are division of the splenic vein and mobilization of the right hemicolon and the mesenteric axis [8]. These procedures allow most patients with PV/SMV resection to undergo reconstruction of the resected PV/SMV by direct end-to-end anastomosis without an interposed graft. However, in our series, there were three patients who required revision of the PV/SMV reconstruction using an interposed graft intraoperatively and two patients with postoperative PV/SMV thrombus after primary end-to-end anastomosis, unless a technical problem such as twist or narrowing at PV/SMV anastomosis in these patients occurs, except for one patient (Fig. 1b). On the contrary, no postoperative PV/SMV thrombus was found in any of the 14 patients treated with PV/SMV reconstruction using a graft. Our results, with regard to the development of PV/SMV thrombus, suggest that the use of a graft in PV/SMV reconstruction in pancreatic resection should be considered preoperatively and/or intraoperatively under the following conditions: (1) the length of the resected PV/SMV is longer than 5 cm in PD; (2) the anastomosis will be performed around the jejunal and iliac branch junction of the SMV, because the wall of the lower SMV is

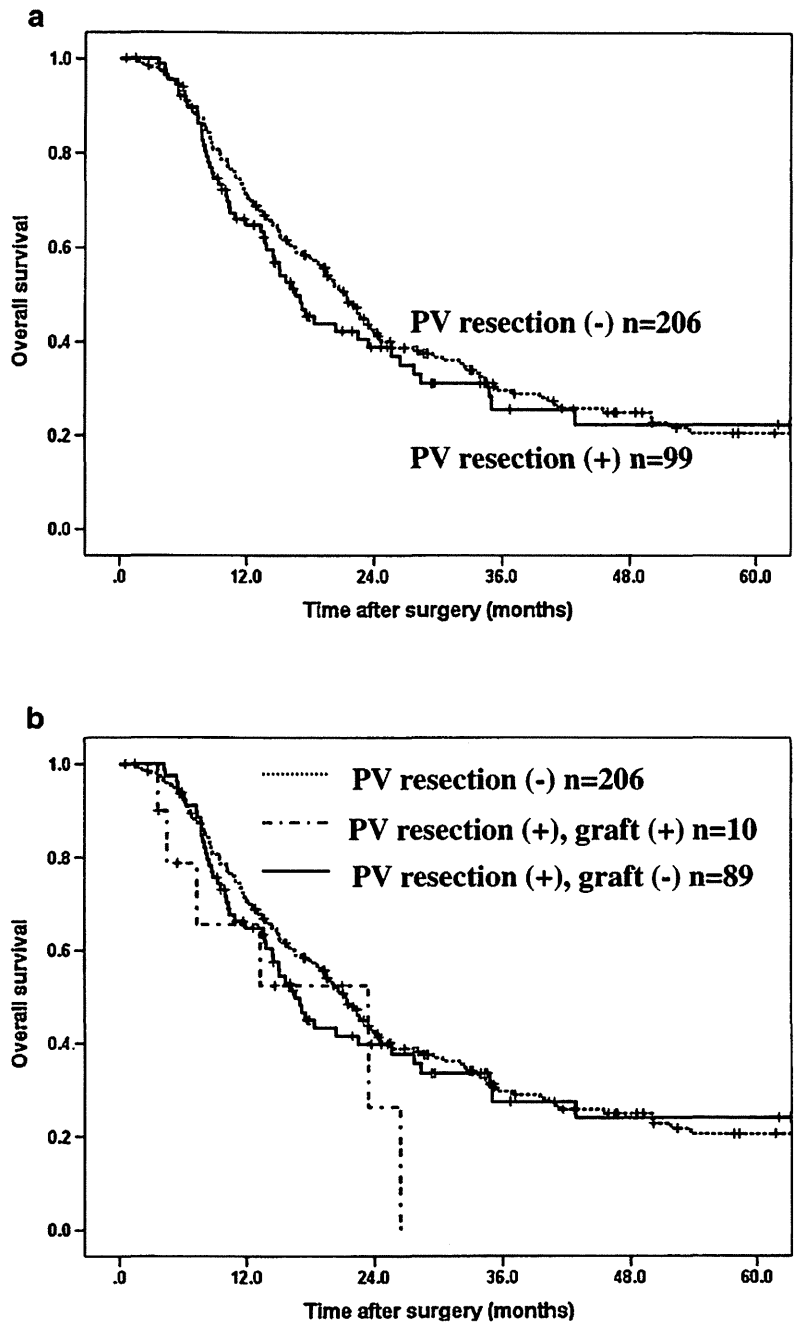

Fig. 2 Kaplan-Meier curves of overall survival (OS) in the patients with pancreatic ductal adenocarcinoma. **a** There was no significant difference in OS comparing the patients with and without portal vein and/or superior mesenteric vein (PV/SMV) reconstruction (P=0.354) and **b** there was also no difference in OS between the patients undergoing PV/SMV reconstruction with and without the use of a graft (P=0.323)

thin and fragile; or (3) both cranial and caudal reconstructed vessels are fixed with the pancreatic head in cases with DP.

There are three major methods for the treatment of acute PV/SMV thrombi: anticoagulation, thrombolytic therapy, and surgical thrombectomy [24–26]. Previous studies reported that only about 50 % of the patients with acute PV/SMV thrombus have a complete recanalization of the PV/SMV with anticoagulation [24, 25]. Surgical thrombectomy has been reported to have high rates of re-thrombosis and a risk of iatrogenic injuries [26]. In our series, the two patients with a postoperative acute PV/SMV thrombus both underwent a successful site-directed thrombolytic therapy.

We performed splenic vein division without reconstruction in 64 patients (64.7 %) undergoing PD, because of tumor invasion of the PV/SMV confluence, and we found no complications due to left-sided portal hypertension. It is possible

that the esophageal vein and established collateral circulation by some preoperative degree of left-sided portal hypertension due to tumor involvement may provide drainage of the spleen and part of the stomach [27]. However, some reports showed that splenic vein ligation induced gastric variceal hemorrhage or thrombocytosis [28–30]. Therefore, further studies are required to clarify this issue.

During the use of a graft in PV/SMV reconstruction, it is important to select a graft with an optimal diameter and length to prevent graft occlusion. A polytetrafluoroethylene graft can match various diameters and lengths for PV/SMV reconstruction, and several recent reports have showed the safety and feasibility similar to autologous vein grafts [9, 10]. Regarding autologous vein grafts, the left renal vein [11–13], EIV [6, 14, 15], IJV [1], and femoral vein [16] can ensure a sufficient diameter and length as intrinsic veins for PV/SMV reconstruction.

For left renal vein grafts, the diameter usually matches well with the PV/SMV, and harvesting it is technically feasible without an additional skin incision during pancreatic resection [11–13]. In our series, in the first patient who required a graft for PV/SMV reconstruction, we attempted to harvest the left renal vein as a graft, but a marked distention of the left kidney was encountered just after clamping the confluence of the left renal vein. Thus, the use of left renal vein grafts may not be feasible in patients with a poor renal or general condition [14, 15]. However, it was reported that the left renal vein graft was successfully used for vascular reconstruction of the PV or inferior *vena cava* without early or long-term renal dysfunction in 14 consecutive patients [12]. Therefore, unsuccessful harvesting of the renal vein, as in our case, may rarely occur. Further studies will be needed.

In the cases of EIV graft, the diameter and length match well with those of the PV/SMV [6, 14, 15]. In addition, the rates of acute deep vein thrombus caused by the ligation of this vein are lower than those of femoral vein grafts, because the lower leg venous flow can return to the inferior *vena cava* through the rotational venous branch [6]. However, leg edema due to deep vein thrombus occurred in some patients (accurate incidence was not provided) in this report [6]. In our series, there were three patients (30 %) with edema of the ipsilateral leg caused by an acute deep vein thrombus after harvesting the EIV for a graft unless they underwent postoperative anticoagulation with intravenous heparin. After these experiences, we decided to change to an IJV graft for PV/SMV reconstruction.

The IJV graft is also an ideal graft for PV/SMV reconstruction, because it has a well-matched diameter and a sufficient length [1]. Moreover, unilateral resection or ligation of an IJV does not cause any venous insufficiency in the head, because of the rich connections between the ipsilateral and contralateral descending veins in the neck [1]. In our series, no patients with PV/SMV reconstruction with an IJV graft had complications related to sacrificing the IJV, and all had a graft patency. Further studies are needed in a larger number of patients to confirm the safety and utility of this graft.

This study had several limitations. The number of the patients with PV/SMV reconstruction with the use of a graft was small compared to that without a graft in this study and, then, it makes very difficult to confirm our suggestions regarding which patients should be treated with grafts and what kind of grafts should be used. It was also difficult to identify independent risk factors in the development of PV/SMV thrombus, because of the small number of patients and to show a survival benefit of this vessel resection because of the short follow-up. Therefore, multicenter data will be needed to assess the risk factors of this aggressive procedure. Moreover, further follow-up study is needed to identify the clinical significance of PV/SMV resection in pancreatic cancer surgery.

In conclusion, the combined resection and reconstruction of the PV/SMV can be carried out without using any graft in most patients. However, depending on the length and/or position of the resected PV/SMV segment, an interposed graft is required for reconstruction in some patients who will undergo (1) the resection of PV/SMV longer than 5 cm in PD, (2) the PV/SMV anastomosis around the jejunal and iliac branch junction of the SMV, or (3) PV/SMV reconstruction in DP. With regard to the autologous graft used in such cases, the IJV may be available in terms of the complications associated with sacrificing the vein, although further studies are needed to confirm our present findings.

Conflicts of interest None.

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Pylorus-Resecting Pancreaticoduodenectomy Offers Long-Term Outcomes Similar to Those of Pylorus-Preserving Pancreaticoduodenectomy: Results of a Prospective Study

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Abstract

Background We showed in a previous study that pylorus-resecting pancreaticoduodenectomy (PrPD), which divides the stomach adjacent to the pylorus ring, preserves more than 95 % of the stomach and significantly reduced the incidence of delayed gastric emptying (DGE) compared with pylorus-preserving pancreaticoduodenectomy (PpPD). However, long-term outcomes of PrPD and the adverse effect of early postoperative DGE on long-term outcomes remain unclear.

Methods A total of 130 patients enrolled in a previous study were followed for 24 months after surgery. Primary endpoint was whether PrPD is a better surgical procedure than PpPD regarding long-term outcomes.

Results Weight loss > grade 2 (Common Terminology Criteria for Adverse Events, Version 4.03) at 24 months after surgery was significantly better in group PrPD (16.2 %) than in group PpPD (42.2 %) ($p = 0.011$). Nutritional status and late postoperative complications were similar for the two groups. The incidence of weight loss > grade 2 at 24 months was 63.6 % in DGE patients with DGE and 25.3 % in non-DGE patients ($p = 0.010$). T_{max} (time to peak $^{13}CO_2$ content in ^{13}C-acetate breath test) at 24 months in DGE patients was significantly delayed compared with that in non-DGE patients (27.9 ± 22.7 vs. 16.5 ± 10.1 min, $p = 0.023$). Serum albumin level at 24 months was higher in non-DGE patients than in those with DGE (3.7 ± 0.6 vs. 4.1 ± 0.4 g/dl, $p = 0.013$).

Conclusions PrPD offers long-term outcomes similar to those of PpPD. DGE may be associated with weight loss and poor nutritional status in patients with long-term outcomes.

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Introduction

We designed pylorus-resecting pancreaticoduodenectomy (PrPD) as a new procedure for periampullary neoplasms [1]. With PrPD, the stomach was divided adjacent to the pylorus ring. Although the pylorus ring was resected, more than 95 % of the stomach was preserved. Our previous randomized controlled trial (RCT), which compared pylorus-preserving pancreaticoduodenectomy (PpPD) and PrPD, demonstrated that PrPD is associated with a significantly lower incidence of delayed gastric emptying (DGE) than is PpPD (4.5 vs. 17.2 %, respectively) in the short term [1]. However, the superiority of PrPD compared with PpPD for long-term outcomes remains unknown. Long-term outcomes after PD have become increasingly important because advances in surgical techniques and perioperative management have led to a low mortality rate and long post-PD survival [2–5]. Therefore, it is important to assess nutritional status, body weight change, and late postoperative complications such as dumping syndrome, diarrhea, and marginal ulcers, which affect quality of life (QOL). To our knowledge, there have been no reports evaluating the long-term outcomes of PrPD.

In previous studies, the incidence of DGE after PD was reported to range from 12 to 42 % [6–10]. Although DGE is not a life-threatening complication, it results in a prolonged length of stay, which contributes to increased hospital costs and decreased QOL [6–10]. How DGE influences long-term outcomes such as nutrition status and

body weight change remains unclear despite DGE being a common complication after PD.

In this study, 130 patients enrolled in our previous RCT were carefully followed for 2 years, and long-term outcomes were compared between two operative procedures. The primary endpoint was whether PrPD is a better surgical procedure than PpPD regarding long-term outcomes. The secondary endpoint was to determine how DGE that occurred during the early period after PD affects long-term outcomes by comparing patients with and without DGE.

Patients and methods

Between October 2005 and March 2009, 139 patients with periampullary tumors were registered [1]. Among them, 130 patients were enrolled in this study, with 64 randomized to PpPD and 66 to PrPD. The Ethics Committee on Clinical Investigation of Wakayama Medical University Hospital (WMUH) approved this study. Informed consent was obtained preoperatively from all participating patients with pancreatic or periampullary lesions at WMUH. Participants also agreed to follow-up for 24 months after surgery. The follow-up was based on clinical, radiologic, and laboratory assessments to evaluate cancer recurrence every 1–3 months after surgery. Subsequent data after tumor recurrence or metastasis were excluded from this analysis.

Surgical procedure

The right gastric artery and vagal nerve were transected at the same levels during both PpPD and PrPD. The right gastric artery was dissected by the root, and the first pyloric branch was dissected along the lesser curvature of the stomach. The first pyloric branch of the right gastroepiploic artery was also dissected along the greater curvature of the stomach. The pyloric branch of the vagal nerve was dissected along with lymph nodes around the pylorus ring. In PpPD the proximal duodenum was divided 3–4 cm distal to the pylorus ring. In PrPD the stomach was divided adjacent to the pylorus ring, with more than 95 % of the stomach being preserved [1] although the pylorus ring was resected. In patients with malignant disease, the following areas of lymph nodes were removed in two procedures: hepatoduodenal ligament, circumferentially around the common hepatic artery, and the right half circumference of the superior mesenteric artery.

All patients underwent PD with the following reconstruction [11]. Pancreaticojejunostomy after PpPD and PrPD was performed by duct-to-mucosa, end-to-side pancreaticojejunostomy in all patients [12]. External suture rows were performed as a single suture between the remnant pancreatic capsule, parenchyma, and jejunal seromuscular area using an interrupted suture with 4-0 Novafil (polybutester; Tyco Healthcare Japan, Tokyo, Japan). Internal suture rows, duct to mucosa, were performed between the pancreatic ductal and jejunal mucosa using eight interrupted sutures with 5-0 PDS-II (polydioxanone; Johnson & Johnson, Tokyo, Japan). Then, an end-to-side hepaticojejunostomy was performed by a one-layer anastomosis (5-0 PDS-II) 10–15 cm distal to the pancreaticojejunostomy. Duodenojejunostomy in PpPD or gastrojejunostomy in PrPD was performed by a two-layer anastomosis (4-0PDS-II and 3-0 silk) via an antecolic route based on the results of our RCT [13] from May 2003 onward.

Postoperative management

A nasogastric tube was inserted prior to surgery and removed from all patients on postoperative day (POD) 1. Oral intake was routinely started on POD 3 or 4. One drain was routinely placed anterior to the pancreaticojejunostomy. If bile leakage and bacterial contamination were absent, this drain was removed on POD 4 in all patients [14]. All patients received an intravenous H_2-blocker (famotidine; Astellas Pharma, Tokyo, Japan) for 2 weeks postoperatively and prophylactic antibiotics every 3 h during surgery. To prevent pancreatic fistula formation or DGE, we did not administer prophylactic octreotide or prokinetic agents such as erythromycin postoperatively. Unless contraindicated by a patient's condition, adjuvant chemotherapy was provided to patients with periampullary or pancreatic carcinoma using the regimen in accord with our protocol based on gemcitabine. H_2-receptor antagonists or proton pump inhibitors were administrated as oral medication for patients with gastrointestinal symptoms such as heartburn or abdominal discomfort.

Follow-up and data collection

Data were collected prospectively for all patients. Assessment of nutritional status by body weight change and serum nutritional parameters was performed before surgery and at 6, 12, 18, and 24 months after surgery. Albumin, prealbumin, transferrin, and retinol-binding protein were measured as serum nutritional parameters. ^{13}C-acetate breath tests at 6, 12, and 24 months after surgery were performed to compare gastric emptying between PpPD and PrPD. Gastric emptying was evaluated by the time to peak $^{13}CO_2$ content (T_{max}) [15–17]. We performed the ^{13}C-labeled mixed triglyceride breath test beyond 24 months after surgery to compare exocrine function between PpPD and PrPD [18].