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Mesenteric approach during pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

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Abstract

Mesenteric approach is an artery-first approach during pancreaticoduodenectomy (PD). In the present study, we evaluated clinical and oncological benefits of this procedure for pancreatic ductal adenocarcinoma (PDAC) of the pancreas head. Between 2000 and 2015, 237 consecutive PDAC patients underwent PD. Among them, 72 experienced the mesenteric approach (mesenteric group) and 165 the conventional approach (conventional group). A matched-pairs group consisted of 116 patients (58 patients in each group) matched for age, gender, resectability status, and neoadjuvant therapy. Surgical and oncological outcomes were compared between the two groups in unmatched- and matched-pair analyses. Intraoperative blood loss was lower in the mesenteric group than in the conventional group in both resectable PDAC (R-PDAC) and borderline resectable PDAC (BR-PDAC) on unmatched- and matched-pairs analyses (R-PDAC, unmatched: 312.5 vs 510 mL, P=.008; matched: 312.5 vs 501.5 mL, P=.023; BR-PDAC, unmatched: 507.5 vs 935 mL, P<.001; matched: 507.5 vs 920 mL, P=.003). Negative surgical margins (R0) and overall survival (OS) rates in the mesenteric group were better in R-PDAC patients (R0 rates, unmatched: 100% vs 87.7%, P=.044; matched: 100% vs 86.7%, P=.045; OS, unmatched: P=.008, matched: P=.021), although there were no significant differences in BR-PDAC patients. Mesenteric approach might reduce blood loss by early ligation of the vessels to the pancreatic head. Furthermore, it might increase R0 rate, leading to improvement of survival for R-PDAC patients. However, R0 and survival rates could not be improved only by the mesenteric approach for BR-PDAC patients. Therefore, effective multidisciplinary treatment is essential to improve survival in BR-PDAC patients.

KEYWORDS

borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC), mesenteric approach, pancreatic ductal adenocarcinoma (PDAC), resectable PDAC (R-PDAC)

1 | INTRODUCTION

In spite of advanced radiographic images, surgical techniques, and chemo(radiation) therapies, the survival rate for pancreatic ductal adenocarcinoma (PDAC) patients is still dismal. Curative treatment for PDAC is considered to be surgical resection only with negative surgical margins (R0) and adjuvant therapies. PDAC tumors without distant metastases were classified into resectable (R-), borderline resectable (BR-), and unresectable PDAC, based on the degree of involvement of the portal vein and/or the superior mesenteric vein (PV/SMV) or major arteries, according to the National Comprehensive Cancer Network (NCCN)[1] and General Rules for the Study of Pancreatic Cancer, 7th edition by the Japanese Pancreatic Society (JPS).[2] Pathological positive margins of resected specimens (R1) could be found not only in BR-PDAC but also in R-PDAC, and might lead to early recurrence and poor survival. Dissected margins around the superior mesenteric artery (SMA) have been specifically reported to be the most favorable R1 site for PDAC located in the pancreatic head.[3–6]

Since the 'artery-first approach' during pancreaticoduodenectomy (PD) was reported in 2010,[7] this term has spread worldwide. The concept of the artery-first approach is to start from the dissection of the connective tissues around the SMA during PD. The aims of this approach are: (i) early determination of the resectability status before committing an irreversible step during operation; (ii) reduction of intraoperative blood loss by early control of blood inflow into the pancreatic head; and (iii) increase of R0 rates by complete dissection of the connected tissues around the SMA.[7–13]

The 'mesenteric approach', first reported by Nakao and Takagi[8] in 1993, is one artery-first approach and is synonymous with the 'infracolic approach'.[11] This approach allows dissection around the SMA from the noncancerous or less inflammatory side at the mesenterium, around the root of the middle colic artery (MCA).[8,9,12,14] Therefore, one should consider that the mesenteric approach may be a safer procedure than other approaches during PD. However, as there have been only a small number of case series reporting the feasibility of the mesenteric approach,[8,9,12,14] evidence for the clinical and oncological benefits of this approach is sparse. In the present study, we evaluated the clinical and oncological outcomes of the mesenteric approach during PD for PDAC of the pancreatic head by comparison with the conventional approach.

2 | METHODS

2.1 | Patients

Between January 2000 and December 2015, 237 consecutive patients underwent PD at Wakayama Medical University Hospital (WMUH) with pathologically proven PDAC. Among them, 72 patients underwent PD with the mesenteric approach between February 2011 and December 2015 (mesenteric group) and the remaining 165 patients underwent PD with the conventional approach between January 2000 and January 2011 (conventional group). We prospectively collected clinicopathological data for patients undergoing PD for PDAC. This retrospective study was approved by WMUH Institutional Review Board (No. 1936) with waived informed consent (UMIN 000026220).

A matched-pairs control group consisted of 116 patients, including 58 patients in the mesenteric group and 58 patients in the conventional group, matched for the following parameters: age, gender, resectability status defined by the NCCN guideline version 2.2016,[1] and administration of neoadjuvant therapy. Unmatched- and matched-pairs analyses were done to compare clinicopathological features, surgical outcomes and oncological outcomes between the two groups.

2.2 | Criteria defining resectability status and regimens of neoadjuvant therapy

Based on multi-detector row computed tomography (MDCT) findings on the initial hospital visit, resectability status was defined according to NCCN guideline version 2.2016.[1] We classified 237 PDAC patients into R-PDAC, BR-PDAC with PV/SMV invasion alone (BR-V PDAC), BR-PDAC with arterial invasion alone (BR-A PDAC), and BR-PDAC with both PV/SMV and arterial invasion (BR-AV PDAC). R-PDAC was defined as a tumor with ≤180° contact of PV/SMV without vein contour irregularity and without contact of major arteries, including the celiac axis, SMA, nor common hepatic artery (CHA). BR-V PDAC was defined as a tumor with >180° contact of PV/SMV or ≤180° contact of PV/SMV with vein contour irregularity. BR-A PDAC was defined as a tumor with contact of CHA without extension to the celiac axis or the hepatic artery bifurcation or ≤180° contact of SMA.[1] BR-AV PDAC was defined as having both criteria of BR-V and BR-A PDAC.

Regimens of neoadjuvant therapy included chemoradiation involving external-beam radiation with 50 Gy in 25 fractions with concurrent S-1 (Taiho, Pharmaceutical Co., Ltd, Tokyo, Japan) at 80 mg/m^2 per day given on alternate days[15] for 6 weeks, and was used between March 2010 and December 2011, and chemotherapy involving concurrent S-1 at 80 mg/m^2 per day with alternate-day administration[15] for 9 weeks and gemcitabine at 800 mg/m^2 on days 1, 8, 22, 29, 43, and 50 was used between January 2012 and December 2014, or modified FOLFIRINOX including 2-hour i.v. infusion of oxaliplatin (Yakult Honsya Co., Ltd, Tokyo, Japan) at 85 mg/m^2 during irrinotecan (Yakult Honsya Co., Ltd) was also i.v. infused over 90 min at 150 mg/m^2, followed by a continuous i.v. infusion of fluorouracil (5-FU) (Kyowa Hakko Kirin Co., Ltd, Tokyo, Japan) over 46 hours at 2400 mg/m^2 every 2 weeks for 8 weeks or 16 weeks between January 2015 and December 2015.[16]

2.3 | Surgical techniques

2.3.1 | Mesenteric approach

We preoperatively evaluated the inferior pancreaticoduodenal artery (IPDA) anatomy including the common trunk composed of the IPDA and the first jejunal artery (J1 artery) arising from the SMA and the IPDA arising directly from the SMA, based on three-dimensional computed tomography (3D-CT) angiography. Furthermore, we measured the distance from the MCA root to the root of the IPDA by

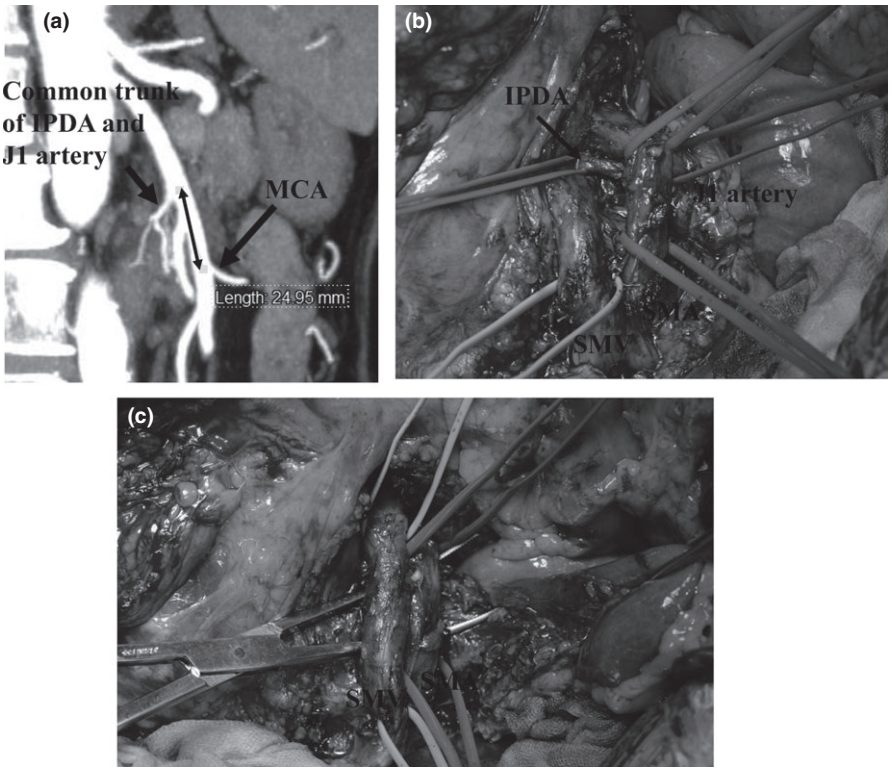

FIGURE 1 (A) Inferior pancreaticoduodenal artery (IPDA) anatomy was evaluated based on three-dimensional computed tomography (3D-CT) angiography. In this case, the common trunk was composed of IPDA and the first jejunal artery (J1 artery) arose from the superior mesenteric artery (SMA). In this case, the distance from the root of the middle colic artery (MCA) to the root of the common trunk of IPDA and J1 artery was approximately 25 mm based on 3D-CT. (B) During dissection of the connective tissue around the SMA, the root of the common trunk of IPDA and J1 artery was identified; it was then ligated and divided. (C) Completion of dissection of the connective tissue around the SMA and superior mesenteric vein (SMV).

3D-CT angiography to easily identify the IPDA root intraoperatively (Figure 1A).

After lifting the transverse colon cranially, the mesenterium was incised from the Treitz ligament to the inferior duodenal flexure to identify the SMA and SMV.[12] The MCA was exposed arising from the anterior side of the SMA, and this artery was usually divided. Dissection of the connective tissues around the SMA started from the left side of the SMA. Distance from the MCA root was intraoperatively measured according to preoperative assessment of the distance measured by 3D-CT (Figure 1A) to identify the origin of the common trunk of the IPDA and the J1 artery or the IPDA directly arising from the SMA. The connective tissue around the SMA containing neurovascular bundle, including the nerve plexus between the SMA and the pancreatic head, was identified as pancreatic head plexus II (plPh-II) by the JPS.[2] Lymph nodes were dissected up to the origin of the SMA in a longitudinal direction (Figure 1B). During this dissection, the IPDA or the common trunk of the IPDA and J1 artery was ligated and divided at the root. The connective tissue around the SMV was then dissected and Henle's gastrocolic trunk and middle colic vein were divided. At this point, dissection around the SMA and SMV was completed (Figure 1C).

After the stomach was divided, lymphadenectomy around the CHA (#8) and root of the left gastric artery (#7), left side of the celiac axis (#9), and in the hepatoduodenal ligament (#12) was carried out. After division of the bile duct, the gastroduodenal artery (GDA) was then ligated and divided. The pancreas was transected, and the pancreas head was abraded from the PV. Finally, the bundle tissues, including nerve plexus, lymph node, and vessels, between the celiac axis and the dorsal surface of the pancreas head were dissected, identified as pancreatic head plexus I (plPh-I) by the JPS.[2] The jejunum was divided, and the tumor with en bloc dissected tissues was removed. If tumor invasion of the PV/SMV was suspected pre- and/or intraoperatively, concomitant resection was carried out immediately before the specimen was removed and reconstruction of PV/SMV.[17] After removal of the specimen, pancreaticojejunostomy, choledocho-jejunostomy, and gastrojejunostomy were carried out in turn.

2.3.2 | Conventional approach

Following Kocher's maneuver, Henle's gastrocolic trunk was divided. After the stomach or duodenum was divided, lymphadenectomy around the same areas as those of the mesenteric approach (#7, #8, #9, and #12) and division of the bile duct were done. The GDA was then divided and the pancreas was transected. The pancreatic head was abraded from the PV/SMV. Finally, exerting traction on the pancreatic head to the right, the plPh-I was dissected from the celiac axis and plPh-II tissues were dissected from the SMA, and the IPDA was divided at this step. After complete isolation of the pancreatic head from the SMA, the jejunum was transected and the specimen was removed. The same reconstruction as that of the mesenteric approach was then carried out.

2.3.3 | Definitions of morbidity and mortality and pathological diagnosis

Criterion for intraoperative transfusion is a hemoglobin value less than 8.0 g/dL and change in vital signs, including low blood pressure and tachycardia, during operation.

Postoperative complications were graded according to the Dindo-Clavien classification.[18] Morbidity was defined as grade III or more based on the Dindo-Clavien classification. Pancreatic fistula was defined and graded according to the International Study Group on Pancreatic Surgery (ISGPS) 2016 criteria,[19] and grades B and C were defined as clinically relevant pancreatic fistula. Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the ISGPS, and DGE was classified into grades A, B, or C, based on the clinical course and postoperative management.[20] Postoperative hospital stay was defined as the duration from the date of operation to the date of discharge. Discharge was allowed after a return to preoperative activities of daily living, no deep-site infections, normal laboratory data, no drains, and the possibility for oral nutrition above basal metabolism. Mortality was defined as death within 90 days after surgery.

Curative resection (R0) was defined as no microscopic evidence of cancer cells along all margins of the resected specimen. We investigated the number of harvested lymph nodes and metastatic lymph nodes.

2.3.4 | Postoperative surveillance and adjuvant therapy

All PDAC patients received postoperative adjuvant chemotherapy, except for those in poor condition or who refused chemotherapy. Regimens of postoperative chemotherapy were either: (i) gemcitabine at 1000 mg/m^2 on days 1, 8, 15 for six cycles; (ii) S-1 at a dose of 80 mg/m^2 for the first 28 conservative days followed by a 14-day rest for four cycles; or (iii) concurrent gemcitabine at 800 mg/m^2 biweekly and S-1 at a dose of 80 mg/m^2 for the first 7 consecutive days followed by a 7-day rest for 6 months.

Patients were followed postoperatively as follows; CT was done every 3 months during postoperative year 1 and every 6 months thereafter. Overall survival (OS) was defined as the time interval from the date of surgery or initial neoadjuvant therapy to either death or the last follow-up date. Recurrence was defined as convincing radiographic evidence of disease during postoperative follow up and was histologically confirmed when possible. Disease-free survival (DFS) was defined as the time interval from the date of surgery to diagnosis of recurrence.

2.4 | Statistical analysis

Summary statistics were calculated with medians and ranges for continuous variables, and frequencies and proportions for categorical variables. Chi-squared tests and Mann-Whitney *U*-test were used to assess differences between treatment groups (mesenteric and conventional groups) and patient characteristics.

Our estimation was a propensity score using a multiple logistic regression model with four covariates: age, gender, resectability status, neoadjuvant therapy. Nearest neighbor paired matching was used to reduce bias resulting from possible imbalance in observed covariates between mesenteric and conventional groups. Matched patients were evaluated for differences between treatment groups in each of the post-operative factors. Moreover, OS and DFS were estimated by the Kaplan-Meier method and they were compared using the log-rank test. Clinicopathological variables were separately compared between R-PDAC patients or BR-PDAC patients undergoing PD with the mesenteric approach and those with the conventional approach. Multivariate analysis was carried out using a Cox proportional hazards regression model, which included variables with $P<.1$ in a univariate analysis. All statistical tests were two-sided, and statistical significance was considered for P values of less than 0.05. All statistical analyses were carried out using the SPSS 20.0 software program (SPSS Inc., Chicago, IL, USA) and JMP version 12.2 (SAS Institute Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Unmatched- and matched-pairs comparative analyses of patients' characteristics between the mesenteric group and the conventional group

When we compared patients' characteristics between mesenteric and conventional groups in unmatched-pairs analysis (Table 1), the incidence of neoadjuvant therapy was higher in the mesenteric group than in the conventional group, although significant differences in other background factors were not found.

In matched-pairs analysis after matching for age, gender resectability status, and administration of neoadjuvant therapy, there were no significant differences in all background factors between the two groups (Table 2).

3.2 | Unmatched- and matched-pairs comparative analyses of perioperative outcomes between the mesenteric group and the conventional group

We compared perioperative outcomes in unmatched- and matched-pairs analyses (Tables 3 and 4). In R-PDAC patients, we found that operative time was longer and intraoperative blood loss was lower in the mesenteric group than in the conventional group in analyses of both unmatched- and matched-pairs (median operative time, unmatched: 417 vs 364 min, $P<.001$ and matched: 416.5 vs 371 min, $P=.007$; median blood loss, unmatched: 312.5 vs 510 mL, $P=.008$ and matched: 312.5 vs 501.5 mL, $P=.023$). Regarding intraoperative transfusion in R-PDAC patients, the frequency was lower in the mesenteric group than in the conventional group in unmatched-pairs analysis (3.3% vs 22.2%, $P=.019$), although the difference did not reach statistical significance in matched-pairs analysis ($P=.055$). Length of hospital stay in R-PDAC patients was shorter in the mesenteric group than in the conventional group in both unmatched- and matched-pairs analyses (median hospital stay, unmatched: 14.5 vs 20 days, $P=.004$ and matched: 14.5 vs 21 days, $P=.007$).

TABLE 1 Comparison of characteristics between PDAC patients undergoing PD with the mesenteric approach and the conventional approach in unmatched-pairs analysis

	R-PDAC patients (n=111)			BR-PDAC patients (n=126)		
	Mesenteric (n=30)	Conventional (n=81)	*P*	Mesenteric (n=42)	Conventional (n=84)	*P*
Age, median (range), years	67 (42-82)	71 (41-91)	.586	68 (48-78)	70 (41-90)	.203
Gender, male, n (%)	19 (63.3)	38 (46.9)	.124	22 (52.4)	45 (53.6)	.900
Serum CA19-9 level, median (range), U/mL	131.3 (2.0-8336.4)	89.6 (1.0-5898.4)	.693	567.2 (2.0-19 755)	318 (1.0-36 979)	.923
Resectability status,[a] n (%)						
R-PDAC	30 (100)	81 (100)		0 (0)	0 (0)	
BR-PDAC	0 (0)	0 (0)		42 (100)	84 (100)	.342
BR-AV	0	0		17 (40.5)	29 (34.5)	
BR-A	0	0		11 (26.2)	33 (39.3)	
BR-V	0	0		14 (33.3)	22 (26.2)	
Tumor size, median (range), mm	23.6 (9.0-31.1)	22.0 (8.0-54.3)	.642	27.1 (10.2-48.0)	26.6 (13.8-48.0)	.881
Neoadjuvant therapy, n (%)	2 (6.7)	0 (0)	.019	21 (50.0)	9 (10.7)	<.001
Follow-up duration, median (range), months	22.5 (4.6-52.4)	20.9 (0.6-135.6)	.936	13.5 (4.7-60.6)	12.0 (1.5-105.4)	.462

CA19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; BR-PDAC, borderline resectable PDAC; BR-A, BR-PDAC with artery involvement; BR-AV, BR-PDAC with artery and portal vein and/or superior mesenteric vein (PV/SMV) involvement; BR-V, BR-PDAC with PV/SMV involvement; R-PDAC, resectable PDAC. [a]resectability status was defined according to National Comprehensive Cancer Network guideline version 2.2016.

TABLE 2 Comparison of characteristics between PDAC patients undergoing PD with the mesenteric approach and the conventional approach in matched-pairs analysis

	R-PDAC patients (n=58)			BR-PDAC patients (n=58)		
	Mesenteric (n=28)	Conventional (n=30)	*P*	Mesenteric (n=30)	Conventional (n=28)	*P*
Age, median (range), years	67 (42-82)	69 (43-87)	.791	70.5 (48-78)	70 (49-79)	.809
Gender, male, n (%)	18 (64.3)	22 (73.3)	.457	15 (50.0)	17 (60.7)	.412
Serum CA19-9 level, median (range), U/mL	135.3 (2.0-8336.4)	139.8 (1.0-5378.0)	.876	525.0 (2.0-19 755)	349.1 (5.9-36 979)	.767
Resectability status,[a] n (%)						
R-PDAC	28 (100)	30 (100)		0 (0)	0 (0)	
BR-PDAC	0 (0)	0 (0)		30 (100)	28 (100)	.894
BR-AV	0	0		10 (33.3)	9 (32.1)	
BR-A	0	0		8 (26.7)	9 (32.1)	
BR-V	0	0		12 (40.0)	10 (35.7)	
Tumor size, median (range), mm	23.6 (9.0-31.1)	22.0 (8.0-37.0)	.539	28.7 (10.2-48.0)	27.3 (16.5-45.0)	.938
Neoadjuvant therapy, n (%)	0 (0)	0 (0)	1.000	9 (30.0)	9 (32.1)	.860
Follow-up duration, median (range), months	22.5 (4.6-52.4)	17.6 (0.6-135.6)	.469	11.7 (4.7-60.6)	13.5 (3.6-105.4)	.635

CA19-9, carbohydrate antigen 19-9; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; BR-PDAC, borderline resectable PDAC; BR-A, BR-PDAC with artery involvement; BR-AV, BR-PDAC with artery and portal vein and/or superior mesenteric vein (PV/SMV) involvement; BR-V, BR-PDAC with PV/SMV involvement; R-PDAC, resectable PDAC. [a]resectability status was defined according to National Comprehensive Cancer Network guideline version 2.2016.

In BR-PDAC patients, operative time was similar in the two groups in matched-pairs analysis (*P*=.210), although it was longer in the mesenteric group in unmatched-pairs analysis (median, 459 vs 432.5 min, *P*=.005). Volume of intraoperative blood loss and frequency of transfusion were lower in the mesenteric group than in the conventional group in both unmatched- and matched-pairs analyses (median blood loss, unmatched: 507.5 vs 935 mL, *P*<.001 and matched: 507.5 vs 920 mL, *P*=.003; transfusion, unmatched: 14.3% vs 57.1%, *P*<.001 and matched: 16.7% vs 46.4%, *P*=.014).

There were no significant differences in morbidity rates, including pancreatic fistula and DGE, and mortality rates and in the frequency of initial administration of adjuvant therapy within 8 weeks after PD between the two groups in both R- and BR-PDAC in unmatched- and matched-pairs analyses (Tables 3 and 4).

TABLE 3 Comparison of perioperative and oncological outcomes between PDAC patients undergoing PD with the mesenteric and the conventional approach in unmatched-pairs analysis

	R-PDAC patients (n=111)			BR-PDAC patients (n=126)		
	Mesenteric (n=30)	Conventional (n=81)	*P*	Mesenteric (n=42)	Conventional (n=84)	*P*
Operative findings						
Portal vein resection, n (%)	12 (40.0)	13 (16.1)	.007	34 (81.0)	43 (51.2)	.001
Operative time, median (range), min	417 (314-535)	364 (241-522)	<.001	459 (348-620)	432.5 (284-651)	.005
Intraoperative blood loss, median (range), mL	312.5 (40-1500)	510 (50-3015)	.008	507.5 (115-2225)	935 (115-6320)	<.001
Transfusion, n (%)	1 (3.3)	18 (22.2)	.019	6 (14.3)	48 (57.1)	<.001
Postoperative complications, ≥grade III,[a] n (%)	5 (16.7)	9 (11.1)	.434	6 (14.3)	15 (17.9)	.612
Mortality, n (%)	0 (0)	1 (1.2)	.541	0 (0)	0 (0)	–
Length of hospital stay, median (range), days	14.5 (10-36)	20 (9-194)	.004	15 (9-59)	20 (9-165)	.020
Pathological findings						
Number of metastatic lymph nodes, n (%)						
None	9 (30.0)	32 (39.5)	.425	10 (23.8)	18 (21.4)	.514
1-3	16 (53.3)	32 (39.5)		15 (35.7)	38 (45.2)	
≥4	5 (16.7)	17 (21.0)		17 (40.5)	28 (33.3)	
No. harvested lymph nodes, median (range)	23 (11-53)	23 (5-64)	.506	27 (10-53)	24 (7-54)	.368
Curative resection R0, n (%)	30 (100)	71 (87.7)	.044	34 (81.0)	58 (69.1)	.156
Adjuvant therapy within 8 weeks after surgery, n (%)	21 (70.0)	43 (53.1)	.109	25 (59.5)	49 (58.3)	.898
Completion of the planned postoperative adjuvant therapy, n (%)	22 (73.3)	38 (46.9)	.013	18 (42.9)	35 (41.7)	.898

DGE, delayed gastric emptying; PD, pancreaticoduodenectomy; PDþAC, pancreatic ductal adenocarcinoma; BR-PDAC, borderline resectable PDAC; R-PDAC, resectable PDAC. [a]postoperative complications were graded according to the Dindo-Clavien classification.

TABLE 4 Comparison of perioperative and oncological outcomes between PDAC patients undergoing PD with the mesenteric and the conventional approach in matched-pairs analysis

	R-PDAC patients (n=58)			BR-PDAC patients (n=58)		
	Mesenteric (n=28)	Conventional (n=30)	*P*	Mesenteric (n=30)	Conventional (n=28)	*P*
Operative findings						
Portal vein resection, n (%)	11 (39.3)	6 (20.0)	.107	24 (80.0)	21 (75.0)	.648
Operative time, median (range), min	416.5 (314-535)	371 (254-520)	.007	459 (374-620)	452 (322-570)	.210
Intraoperative blood loss, median (range), mL	312.5 (40-1500)	501.5 (60-2230)	.023	507.5 (115-2225)	920 (115-3610)	.003
Transfusion, n (%)	1 (3.6)	6 (20.0)	.055	5 (16.7)	13 (46.4)	.014
Postoperative complications, ≥grade III,[a] n (%)	5 (17.9)	3 (10.0)	.386	4 (13.3)	5 (17.9)	.634
Mortality, n (%)	0 (0)	1 (3.3)	.330	0 (0)	0 (0)	–
Length of hospital stay, median (range), days	14.5 (10-36)	21 (11-65)	.007	15 (9-59)	17.5 (10-42)	.863
Pathological findings						
Number of metastatic lymph nodes, n (%)						
None	7 (25.0)	14 (46.7)	.229	6 (20.0)	6 (21.4)	.114
1-3	16 (57.1)	12 (40.0)		9 (30.0)	15 (53.6)	
≥4	5 (17.9)	4 (13.3)		15 (50.0)	7 (25.0)	
No. harvested lymph nodes, median (range)	23 (11-53)	23.5 (11-48)	.919	26.5 (10-53)	26 (9-49)	.668
Curative resection R0, n (%)	28 (100)	26 (86.7)	.045	24 (80.0)	24 (85.7)	.565
Adjuvant therapy within 8 weeks after surgery, n (%)	19 (67.9)	17 (56.7)	.380	18 (60.0)	14 (50.0)	.444
Completion of the planned postoperative adjuvant therapy, n (%)	20 (71.4)	16 (53.3)	.156	12 (40.0)	10 (35.7)	.737

DGE, delayed gastric emptying; PD, pancreaticoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; BR-PDAC, borderline resectable PDAC; R-PDAC, resectable PDAC. [a]postoperative complications were graded according to the Dindo-Clavien classification.

3.3 | Unmatched- and matched-pairs comparative analyses of oncological outcomes between the mesenteric group and the conventional group

Numbers of harvested or metastatic lymph nodes were similar between the two groups in R- and BR-PDAC in both analyses (Tables 3 and 4). However, the rate of R0 resection was significantly higher in the mesenteric group in R-PDAC patients in both unmatched- and matched-pairs analyses (unmatched: 100% vs 87.7%, *P*=.044 and matched: 100% vs 86.7%, *P*=.045), although there were no significant differences in the R0 rate in BR-PDAC in both analyses.

Incidence of postoperative recurrence was similar in both R- and BR-PDAC patients in matched-pairs analysis, although all recurrence rates and local recurrence rates in R-PDAC patients were lower in the mesenteric group in unmatched-pairs analysis (all recurrence: 53.3% vs 77.8%, *P*=.012, local recurrence: 16.7% vs 38.3%, *P*=.031, Figure 2). OS was longer in the mesenteric group than in the conventional group in R-PDAC patients in both unmatched- and matched-pairs analyses (unmatched: *P*=.008, Figure 3A, matched: *P*=.021, Figure 3B), although there were no significant differences in DFS between the two groups in R-PDAC patients in both analyses. In BR-PDAC patients, OS and DFS were similar in the two groups in both analyses (Figure 3C, D).

3.4 | Identification of risk factors for poor survival for R-PDAC and BR-PDAC patients

We investigated the risk factors associated with poor OS and DFS in all R-PDAC (n=111) or BR-PDAC patients (n=126). In R-PDAC patients, we found six factors for poor OS on univariate analysis: jaundice (*P*=.003), tumor size more than 30 mm (*P*=.024), conventional approach (*P*=.008), transfusion (*P*=.021), lymph node metastasis (*P*<.001), and no completion of the planned postoperative adjuvant therapy (*P*<.001). Multivariate analysis showed that lymph node metastasis (*P*<.001, odds ratio [OR]; 4.032, 95% confidence intervals [CI]; 2.580-9.048) and no completion of the planned postoperative adjuvant therapy (*P*<.001, OR; 4.587, 95% CI; 2.472-8.511)

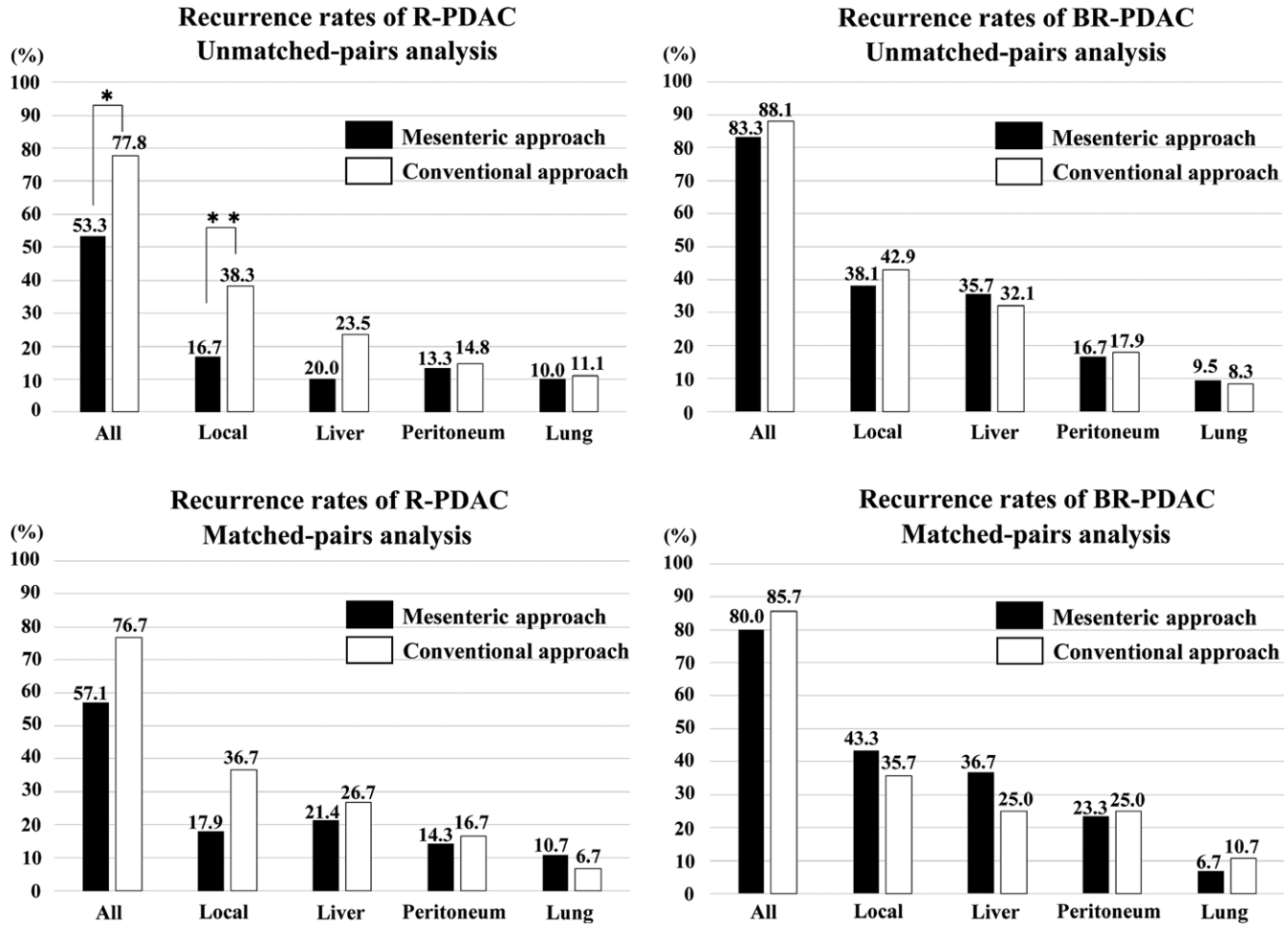

FIGURE 2 Recurrence rates of resectable pancreatic ductal adenocarcinoma (R-PDAC) and borderline resectable PDAC (BR-PDAC) patients in unmatched- and matched-pairs analyses. All recurrence rates and local recurrence rates were significantly lower in the mesenteric group than in the conventional group in unmatched-pairs analysis only (*all recurrence: 53.3% vs 77.8%, *P*=.012; **local recurrence: 16.7% vs 38.3%, *P*=.031).

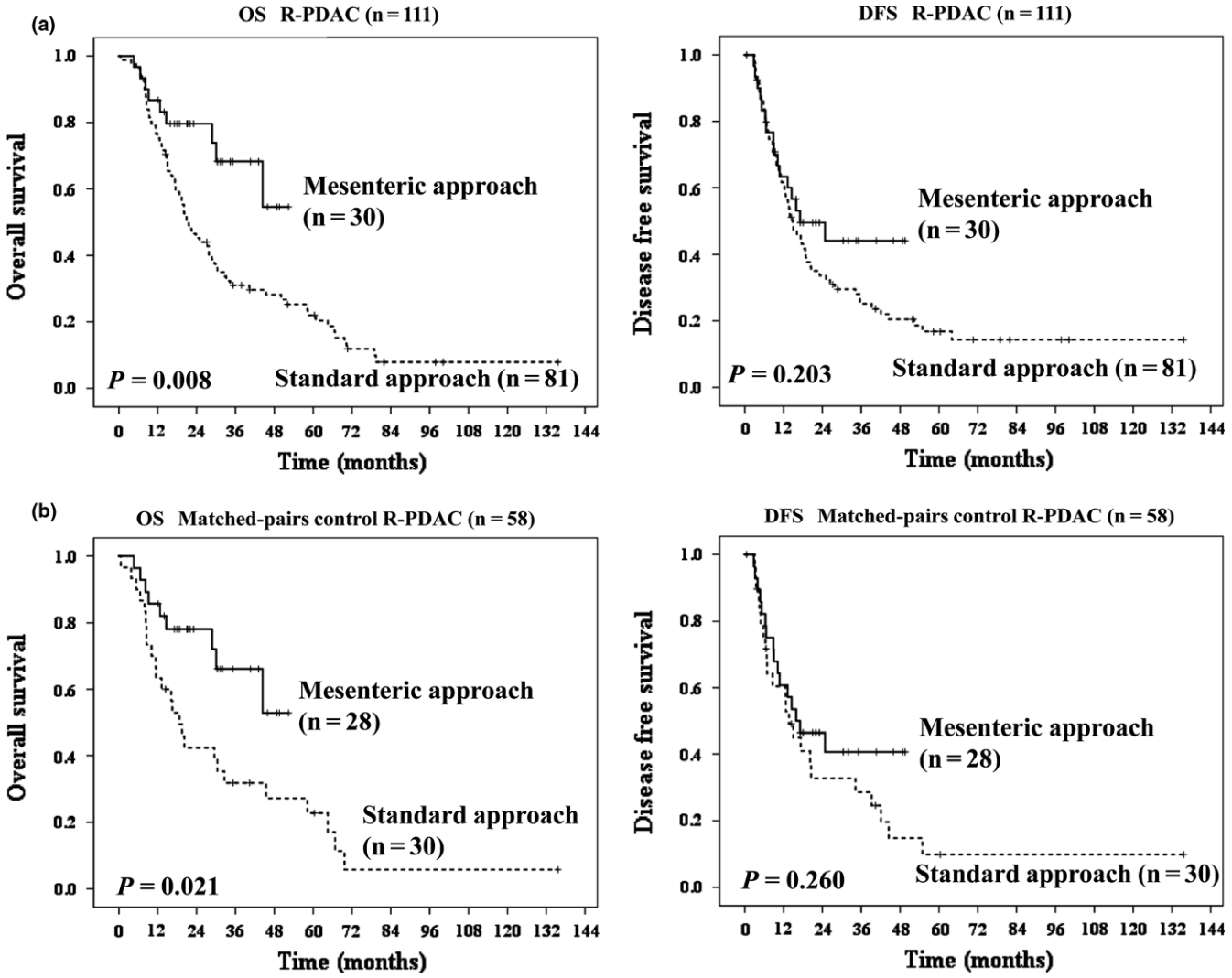

FIGURE 3 (A) Overall survival (OS) for resectable pancreatic ductal adenocarcinoma (R-PDAC) patients in unmatched-pairs analysis was longer in the mesenteric group than in the conventional group (*P*=.008), although the disease-free survival (DFS) was similar in the two groups. (B) OS for R-PDAC patients in matched-pairs analysis was also longer in the mesenteric group than in the conventional group (*P*=.021), although there was no significant difference of DFS. (C) There were no significant differences of both OS and DFS in borderline resectable PDAC (BR-PDAC) patients in unmatched-pairs analysis. (D) There were no significant differences of both OS and DFS in BR-PDAC patients in matched-pairs analysis.

were independent risk factors. Regarding DFS in R-PDAC patients, we found four risk factors for poor DFS on univariate analysis; jaundice (*P*=.011), tumor size more than 30 mm (*P*=.002), lymph node metastasis (*P*<.001), and no completion of the planned postoperative adjuvant therapy (*P*=.001). Furthermore, moderate or poorly differentiated adenocarcinoma (*P*=.005, OR: 1.996, 95% CI: 1.227-3.247), lymph node metastasis (*P*<.001, OR: 6.002, 95% CI: 3.155-11.416), and no completion of the planned postoperative adjuvant therapy (*P*<.001, OR: 3.555, 95% CI: 2.142-5.900) were independent risk factors for poor DFS for R-PDAC patients on multivariate analysis.

In BR-PDAC patients, elevated serum CA19-9 level (*P*=.029), transfusion (*P*=.045), and no completion of the planned postoperative adjuvant therapy (*P*<.001) were risk factors for poor OS on univariate analysis, and we found two independent factors on multivariate analysis: elevated serum CA19-9 level (*P*=.042, OR: 1.648, 95% CI: 1.017-2.671), and no completion of the planned postoperative adjuvant therapy (*P*<.001, OR: 2.672, 95% CI: 1.810-3.944). Furthermore, elevated serum CA19-9 level (*P*=.006, OR: 1.966, 95% CI: 1.209-3.198) and no completion of the planned postoperative adjuvant therapy (*P*<.001, OR: 2.635, 95% CI: 1.757-3.953) were independent risk factors associated with poor DFS.

4 | DISCUSSION

Connective tissue between the pancreatic head and the SMA plexus has been defined as pancreatic head plexus II (plPh-II), but is also known as 'mesopancreas'[10,21,22] or 'meso-pancreatoduodenum'.[23]

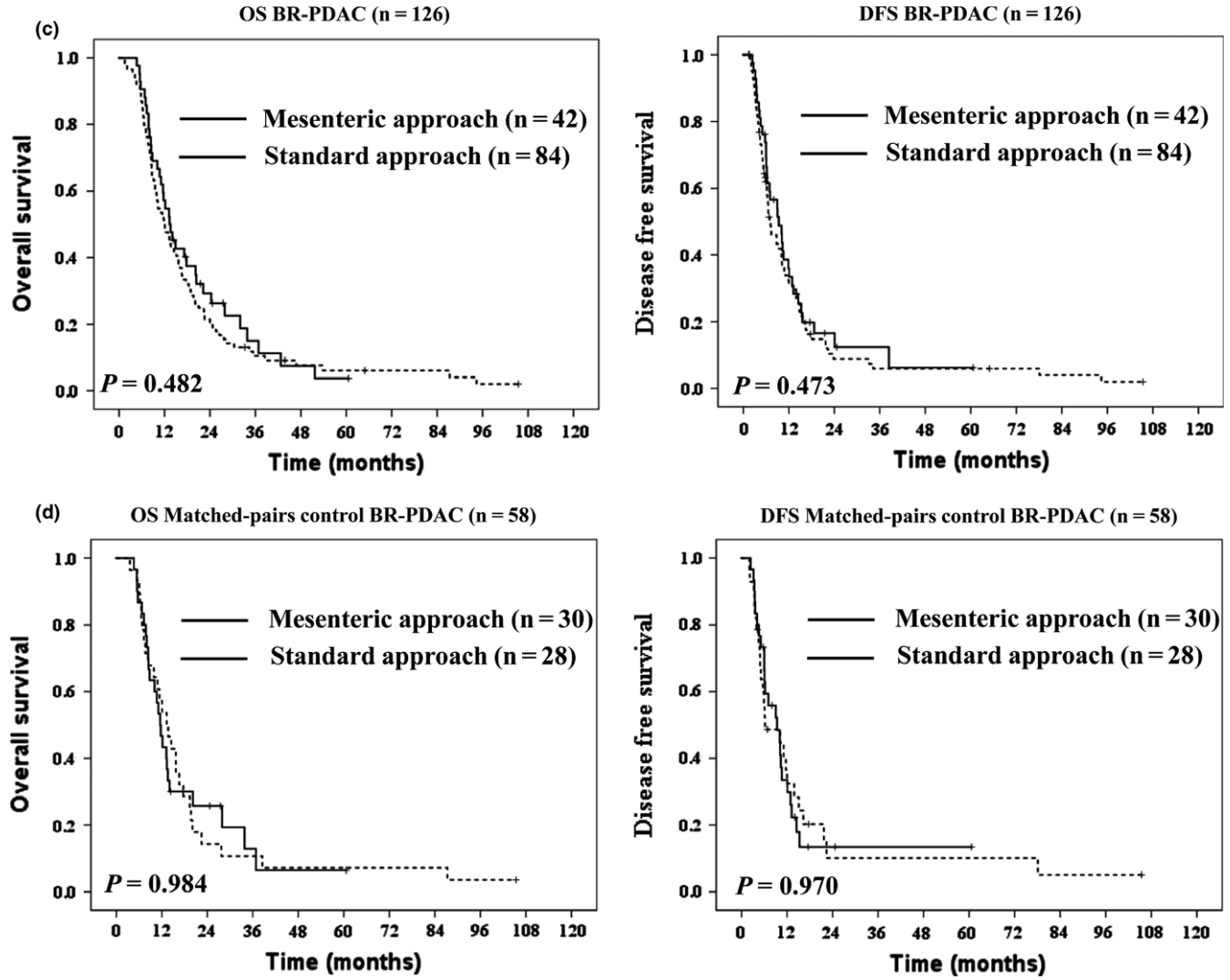

FIGURE 3 Continued.

However, from an anatomical point of view, this nomenclature is controversial.[24] The dissected margin of plPh-II is reported to be the most favorable positive margin site for PDAC of the pancreatic head.[3–6] Therefore, complete clearance of the connective tissue around the SMA during PD is considered to increase R0 rate and improve the survival rate of patients with PDAC located in the pancreatic head.[8–10,12,13,21–23,25] Furthermore, the artery-first approach aims to assess resectability status before irreversible steps in the operation and reduce blood loss as a result of early ligation of the vessels to the pancreatic head. However, a limited case series that reported the feasibility of the artery-first approach during PD has found little evidence of the availability and/or oncological benefits of this procedure.[10,13,14,23,24] The mesenteric approach, which is one of the artery-first approaches during PD,[8,9,12] is considered to be a safer procedure because, in this approach, dissection around the SMA starts from an infracolic noncancerous and/or no inflammatory region toward the root of the SMA. Therefore, since 2011, we have carried out the mesenteric approach for PDAC. In the present study, we evaluated the perioperative and oncological outcomes of this approach compared with those of the conventional approach.

When we compared the backgrounds of the mesenteric and conventional groups, the rate of administration of neoadjuvant therapy was significantly higher in the mesenteric group, as a result of the different time periods of each approach. Therefore, we selected 58 patients with the mesenteric approach and 58 patients with the conventional approach based on a 1:1 matching scheme based on age, gender, resectability status, and administration of neoadjuvant therapy. We had to consider factors that may have had an implication for perioperative and oncological outcomes in order to remove background bias of the two groups. We compared the clinicopathological features between the two groups in both unmatched- and matched-pairs analyses.

Regarding perioperative outcome, we found that operative time was longer in the mesenteric group than in the conventional group in R-PDAC, and the volume of intraoperative blood loss was lower in both R-PDAC and BR-PDAC, and the incidence of transfusion

was lower in BR-PDAC in both unmatched- and matched-pairs analyses. The reason for the longer time in the mesenteric group may be associated with the learning curve of operation. Our results indicate that the mesenteric approach might reduce intraoperative blood loss by early ligation of vessels flowing into the pancreatic head, and it may lead to a decrease in the incidence of transfusion. Although we found that the frequency of postoperative complications was similar in the two groups, the length of the hospital stay was shorter in the mesenteric group in R-PDAC patients. The frequencies of administration of adjuvant therapy within 8 weeks after surgery and completion of the planned postoperative adjuvant therapy were not different in the two groups in both matched R-PDAC and BR-PDAC patients. However, the regimens of postoperative adjuvant therapy in the mesenteric and conventional groups were different even in matched-pairs analyses, in which gemcitabine was dominant for the conventional group and S-1 was dominant for the mesenteric group (R-PDAC; P=.002 and BR-PDAC; P=.080), and this historical bias is a huge problem for survival analysis in the present study.

Regarding oncological outcome, we found that the R0 rate was higher in the mesenteric group than in the conventional group in R-PDAC patients. However, there was no significant difference between the two groups in BR-PDAC patients in unmatched- and matched-pairs analyses. These results indicated that the mesenteric approach for R-PDAC in the pancreatic head might increase R0 rate by complete dissection of connective tissues around the SMA, and this procedure might lead to improvement of survival for R-PDAC patients. However, in the present study, the mesenteric approach alone could not improve the R0 rate as well as the survival of BR-PDAC patients. Therefore, one should consider that effective neoadjuvant therapy may be necessary to increase the R0 rate, and multimodality treatment may be essential to improve survival of BR-PDAC patients.

This study has several limitations. It includes a retrospective cohort with a small sample size at a single institution. Selection bias may have occurred, particularly with respect to operative indications and variations in preoperative examinations and operations between physicians, surgeons, and institutional characteristics. Furthermore, we compared the surgical and oncological outcomes between the mesenteric group and the conventional group, but some backgrounds of the two groups were different. Although we analyzed them in matched-pairs control patients to remove the bias as much as possible, the historical bias remained. The dominant regimen of postoperative adjuvant therapy was also different in the two groups even after the pair-matched propensity score approach in which S-1 was dominant in the mesenteric group and gemcitabine was dominant in the conventional group. Therefore, randomized clinical trials (RCT) are needed to compare surgical and oncological outcomes between the mesenteric approach and the conventional approach; we plan to start this RCT soon.

In conclusion, the mesenteric approach might reduce blood loss during PD by early ligation of vessels to the pancreatic head in both R- and BR-PDAC patients, leading to low frequency of transfusion. Complete clearance around the SMA by the mesenteric approach might increase the R0 rate for R-PDAC patients, leading to a decrease in the recurrence rate and improvement of the survival rate. However, this procedure alone may not be sufficient to increase R0 rate, decrease recurrence rate, and improve survival in BR-PDAC patients. Therefore, effective multidisciplinary treatment is essential to improve survival in BR-PDAC patients. Large prospective studies are necessary to confirm the results of the present study.

DISCLOSURE

Conflict of Interest: Authors declare no conflicts of interest for this article.

Author Contributions: Yamaue and Hirono had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hirono, Kawai, Shimokawa, Nakao, Yamaue. Acquisition or interpretation of data: Hirono, Okada, Miyazawa, Ueno, Shimokawa. Draft of the manuscript: Hirono, Kawai, Shimokawa, Yamaue. Critical revision of the manuscript for important intellectual content: Hirono, Nakao, Yamaue. Administrative, technical, or material support: Hirono, Kawai, Okada, Miyazawa, Shimizu, Kitahata, Shimokawa, Yamaue. Study supervision: Shimokawa, Nakao, Yamaue.

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