



Ischemic gastropathy after distal pancreatectomy with en bloc celiac axis resection for pancreatic body cancer

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Abstract

Purpose Risk factors of ischemic gastropathy (IG) following distal pancreatectomy with en bloc celiac axis resection (DP-CAR) remain unclear.

Methods Fifty consecutive patients with pancreatic cancer who underwent DP-CAR were retrospectively reviewed for possible risk factors for IG. This study was registered on the UMIN Clinical Trials Registry (UMIN 000028732).

Results Complications higher than grade 3 were observed in 21 patients (42%) and mortality in 4 (8%). Left gastric artery (LGA) resection ($P = 0.046$) and a combination of left inferior phrenic artery (IPA) with LGA resection ($P = 0.012$) were risk factors of IG, and an elevated creatine kinase (CK) value ≥ 1005 IU/L ($P = 0.025$) was associated with IG. Among prognostic factors, IG (OR, 5.997; 95% CI, 1.543–23.309; $P = 0.010$), completion of adjuvant chemotherapy (OR, 0.282; 95% CI, 0.121–0.654; $P = 0.003$), longer operative time (OR, 2.261; 95% CI, 1.084–4.714; $P = 0.030$), and higher age (OR, 2.212; 95% CI, 1.081–4.524; $P = 0.030$) remained independent predictors of survival. Comparison at 2 and 3 months postoperatively showed nutritional values were higher in patients who underwent LGA-preserving DP-CAR than those with LGA-resecting DP-CAR: total protein (7.17 ± 0.56 vs 6.65 ± 0.66 g/dl, $P = 0.007$), albumin (4.04 ± 0.45 vs 3.43 ± 0.43 g/dl, $P < 0.001$), and total cholesterol (162.3 ± 34.7 vs 141.6 ± 27.2 mg/dl, $P = 0.044$).

Conclusions The poorer prognosis in patients who undergo DP-CAR may be related to more advanced tumors. A combination of left IPA and LGA resection was a significant risk factor for IG. IG, completion of adjuvant chemotherapy, longer operative time, and higher age remain good independent predictors of survival.

Keywords Ischemic gastropathy · Inferior phrenic artery · Celiac axis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with poor prognosis and is predicted to be the second leading

common cause of cancer-related mortality worldwide by 2030 [1]. Curative surgical resection with adjuvant therapy is considered the best option for longer survival [2]. Most pancreatic adenocarcinomas recur systemically, so tumors

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involving vascular structures recur frequently, even following aggressive surgery. As stronger chemotherapy is being introduced as a neoadjuvant therapy [3], combined arterial resection should be revisited [4], and a decision should be made regarding conversion surgery. The Appleby operation has been modified for safety and has re-emerged as a focus of pancreatic surgeons as a radical pancreatectomy for locally advanced/borderline resectable pancreatic body/tail carcinoma [5–7]. The modified Appleby operation, a synonym for distal pancreatectomy with en bloc celiac axis resection (DP-CAR), is a procedure enabling removal of T4 pancreatic body/tail carcinoma. Until now, in ordinary clinical settings, these have had unresectable status. More favorable prognosis is expected by increasing the R0 resection rate in T3 cases, taking a wider surgical margin. Moreover, cancer-related pain relief can be achieved by removal of tumors infiltrating plexuses [8, 9].

DP-CAR remains a controversial procedure because of unsolved issues, including ischemic complications of the stomach in the early postoperative period, and whether the procedure has genuine long-term survival benefits for patients with pancreatic cancer. In particular, the ischemic gastropathy (IG) after DP-CAR can sometimes become a severe and prolonged complication. In spite of this, the clinical impact of IG has not been sufficiently discussed. Several sources have reported the challenge in development of this procedure based on experience of severe complications in clinical studies [10, 11]. Incidences of morbidity and mortality remain high compared to other pancreatectomies [12].

In our institution, based on our initial experience of IG, we demonstrated that the LGA can be preserved in cases with LGA branches antecedently and those where the distance between the LGA and the tumor is more than 10 mm [9]. In patients who undergo DP-CAR, resection of LGA is an independent risk factor for delayed gastric emptying (DGE) [13].

This study was approved by the Wakayama Medical University Hospital Institutional Review Board (No. 2066) and was registered on the UMIN Clinical Trials Registry (UMIN 000028732).

By analyzing the clinicopathological data of patients who have undergone DP-CAR, this study aims to clarify risk factors and clinical impact of IG.

Patients and methods

Patients

Enrolled in this study were 50 consecutive patients who underwent DP-CAR between October 2004 and May 2017 at Wakayama Medical University Hospital (Table 1). We investigated the risk factors for IG and performed analysis to identify prognostic indicators among these patients. No patients underwent preventive total gastrectomy to avoid gastric ischemic complications during DP-CAR. Pathologic stages

were diagnosed according to the Union for International Cancer Control (UICC) seventh tumor-node-metastasis (TNM) classification [14]. Based on pathological diagnosis of the resected specimen, microscopic surgical margin status (R0 or R1) was examined. We defined R0 status as the absence of tumor cells within 1 mm of the resection margin and R1 status as the presence of tumor cells within 1 mm of the resection margin [15]. Until February 2010, upfront surgery was used but gave low R0 rates [9]. Since March 2010, our current treatment has included neoadjuvant therapy for all patients who are indicated for DP-CAR. In this study, borderline resectable pancreatic cancer (BRPC) was reviewed and defined according to National Comprehensive Cancer Network (NCCN) criteria version 2.2015 [16]. Routine preoperative endoscopic examination confirmed normal status of gastroduodenal mucosa in all patients. Patients underwent postoperative endoscopic examination if they presented gastrointestinal symptoms or required endoscopic intervention.

Preoperative arterial embolization

Preoperative arterial embolization was routinely performed for developing the blood flow via the pancreatic head arcade about a week prior to surgery to prevent ischemic complications of the liver and the stomach after DP-CAR. In patients who were to undergo LGA-resecting DP-CAR (conventional DP-CAR), arterial embolization was performed using interlocking detachable coils (IDCs) [17] in the celiac axis (CA), the common hepatic artery (CHA), and the left gastric artery (LGA) (Fig. 1a). In patients who were to undergo LGA-preserving DP-CAR (modified DP-CAR), arterial embolization was performed in only the CHA distal side of LGA branch (Fig. 1b).

Neoadjuvant therapy

In our institution, patients with BRPC underwent neoadjuvant therapy as follows: between March 2010 and December 2011, patients with BRPC underwent neoadjuvant chemoradiation therapy involving external-beam radiation with 50 Gy plus concurrent alternate-day oral therapy with S-1 for 6 weeks [18]; between January 2012 and December 2013, neoadjuvant chemotherapy involving concurrent alternate-day oral therapy with S-1 and gemcitabine for 9 weeks [18]; between April 2014 and May 2015, modified FOLFIRINOX (without bolus 5-FU and LV, also decreased dose of irinotecan; FIRINOX) by 4 or 8 cycles repeated every 2 weeks [19]; and from July 2015, nab-paclitaxel plus gemcitabine for 8 weeks [20]. In cases with no disease progression, patients underwent DP-CAR within 4 weeks.

Surveillance and postoperative adjuvant therapy

Patients who had undergone surgery were expected to receive adjuvant therapy. Follow-up surveillance was performed as

Table 1 Clinical and operative characteristics of patients (*n* = 50)

Patients	
Age, years	68 (49–79)
Sex, man/woman	32 (64%)/18 (36%)
BMI (kg/m ²)	22 (17–29)
ASA-PS, class 1/2/3/4/5	2 (4%)/39 (78%)/9 (18%)/0/0
Preoperative arterial embolization	46 (92%)
Neoadjuvant therapy	26 (52%)
Tumor marker	
CEA	2.3 (0.1–14.0)
CA19-9	106.0 (0–6382)
DUPAN-2	88.5 (0–25,450)
Operative	
Operative time (min)	342 (136–846)
Blood loss (mL)	500 (20–9900)
Blood transfusion	10 (20%)
Combined resection	
Portal vein	13 (26%)
Other organ (jejunum/colon/stomach/left adrenal gland/left kidney)	2 (4%)/2 (4%)/1 (2%)/22 (44%)/1 (2%)
Optional procedure	
Cholecystectomy	24 (48%)
Pancreaticojejunostomy for pancreatic stump	17 (34%)
LGA preservation	23 (46%)
Tumor characteristics (pathological stage, UICC (7th, 2009))	
Tumor size (mm)	30 (1–93)
Primary tumor	
T1, T2	1 (2%)
T3	43 (86%)
T4	6 (12%)
Lymph node metastasis	
N0	19 (38%)
N1	31 (62%)
Stage	
IIA	19 (38%)
IIB	24 (48%)
III	6 (12%)
IV	1 (2%)
Histopathologic type	
Well-moderate differentiated	43 (86%)
Poorly differentiated	5 (10%)
Other	2 (4%)
Residual tumor status	
R0 (overall/neoadjuvant therapy/upfront surgery)	31 (62%)/20 (81%)/11 (42%)
R1, 2 (overall/neoadjuvant therapy/upfront surgery)	19 (38%)/5 (19%)/14 (58%)

Values are median (range) or number (percentage), unless otherwise stated

BMI body mass index, *ASA-PS* American Society of Anesthesiologists-Physical Status, *UICC* Union for International Cancer Control, *LGA* left gastric artery, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen, *DUPAN-2* pancreatic cancer-associated antigen

reported previously [18]. Postoperative adjuvant chemotherapy regimens also differed depending on the timing. Between

October 2004 and August 2013, gemcitabine was taken intravenously based on the CONKO-001 study [21] with or

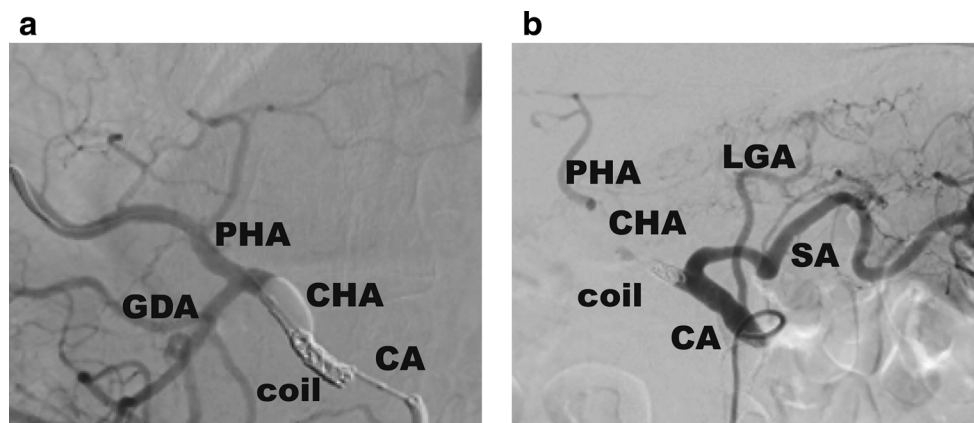


Fig. 1 Angiography examination showing arterial embolization performed using interlocking detachable coils in the celiac axis (CA), the common hepatic (CHA), and the left gastric arteries (LGA) in patients who were intended to undergo conventional DP-CAR (a),

performed in only in the CHA distal side of LGA branch in patients who were intended to undergo modified DP-CAR (b). CA: celiac axis, CHA: common hepatic artery, PHA: proper hepatic artery, GDA: gastroduodenal artery, LGA: left gastric artery, SA: splenic artery

without concurrent alternate-day oral therapy with S-1 [22]. From September 2013, oral therapy was undertaken with S-1 based on the JASPAC 01 study [23].

Surgical procedures

Indications and surgical procedures used during conventional DP-CAR were similar to those previously reported [9] (Fig. 2a). DP-CAR was applied in patients with tumors invading the plexus around the common hepatic artery, the root of the splenic artery, or the CA. Patients who had antecedent branching of the LGA and had a distance between the LGA and carcinoma greater than 10 mm underwent modified DP-CAR, where the artery was divided just below the branching of the LGA, as we previously reported [13, 24] (Fig. 2b). In all cases, nerve plexuses and lymph nodes in proximal portion along the SMA through the perineural spaces were also dissected. The left gastric veins and the posterior gastric vein were divided in all cases. In this series, the gastroduodenal arteries and the right gastric and right gastroepiploic arteries

were identified and preserved in all cases. Based on the experience of patient-presented ischemic cholecystitis after DP-CAR, we have routinely performed cholecystectomy as a concomitant procedure since 2011.

We conducted a single center pilot study [10] and a multicenter randomized control trial (RCT) of pancreaticojejunostomy (PJ) with 17 patients [11] to evaluate whether pancreatic stump decreases the incidence after distal pancreatectomy (DP)/DP-CAR.

Investigation of the postoperative stomach blood flow

In the present study, elimination of the left inferior phrenic arteries (IPA) was investigated by postoperative computed tomography (CT) to compare/review preoperative images [25] and operative records as a risk factor of organ ischemia. The blood flow status postconventional DP-CAR with bilateral IPA combined resection is illustrated in Fig. 3.

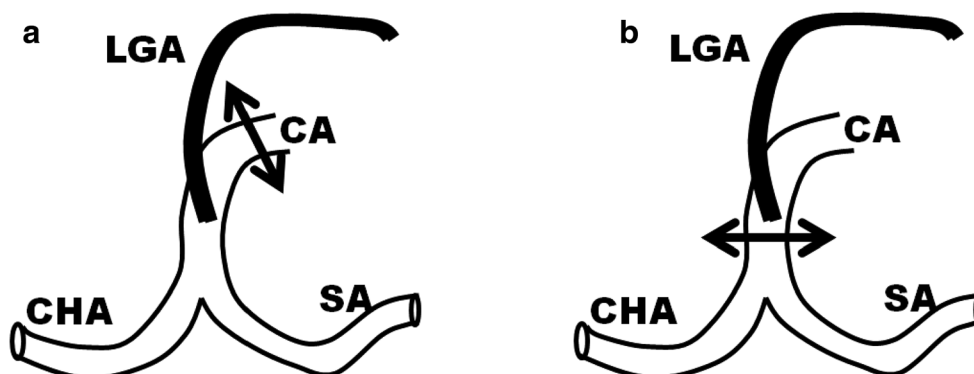
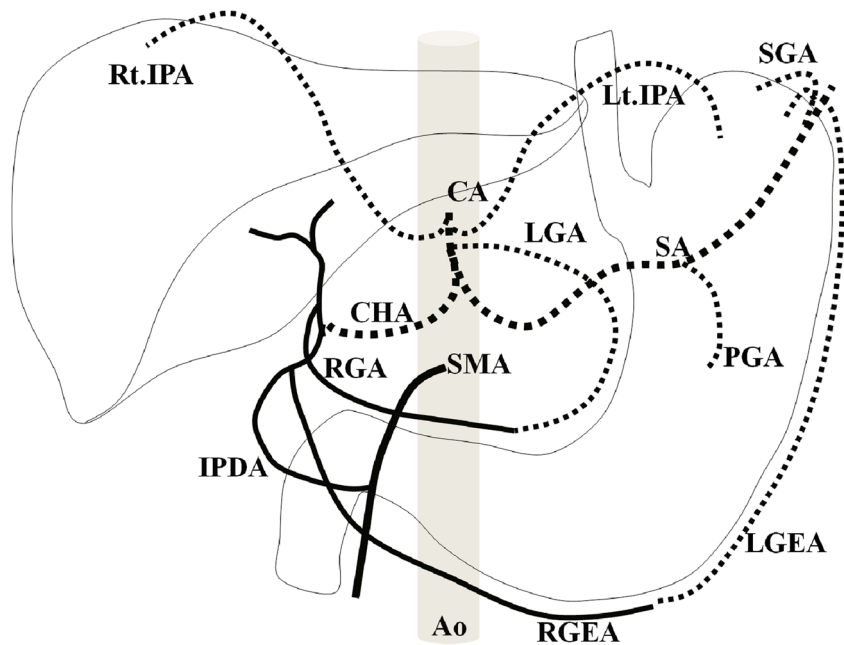


Fig. 2 Schema showing the relationship between the division site and the branching site of the left gastric artery (a) in conventional DP-CAR and (b) in distal pancreatectomy with resection of the common hepatic and splenic artery, with preservation of the left gastric artery (modified DP-

CAR). Double-headed arrows indicate the site of the division. CA: celiac axis, SA: splenic artery, CHA: common hepatic artery, LGA: left gastric artery

Fig. 3 Blood flow status after conventional DP-CAR with bilateral IPA combined resection. Solid lines represent arteries with blood flow and dotted lines represent arteries without blood flow after surgery. Ao: aorta, CA: celiac axis, SA: splenic artery, CHA: common hepatic artery, SMA: superior mesenteric artery, LGA: left gastric artery, RGA: right gastric artery, IPDA: inferior pancreaticoduodenal artery, RGEA: right gastroepiploic artery, LGEA: left gastroepiploic artery, PGA: posterior gastric artery, SGA: short gastric artery, Rt IPA: right inferior phrenic artery, Lt IPA: left inferior phrenic artery



Investigation of the early phase nutritional status

To confirm the nutritional impact of single factors of LGA preservation, we investigated the preoperative/postoperative body weight/laboratory data including total protein (TP), albumin (Alb), and total cholesterol (TC) as nutrition-related factors. We compared them between the groups with conventional DP-CAR and modified DP-CAR. Preoperative data was defined as those obtained within 2 weeks before surgery, even in patients who underwent neoadjuvant therapy. Postoperative data was determined as those with highest values between postoperative months 2 and 3. We selected this postoperative period to remove the effect of potential cancer recurrence as much as possible without data loss.

Definition of postoperative complications

We defined DGE according to consensus and the clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS) [26]. Definition of pancreatic fistula was set according to ISGPS guidelines [27]. Postpancreatic hemorrhage was also defined by the ISGPS [28]. IG was defined by gastroduodenal ulcer or perforation due to ischemic change of the gastric wall identified by endoscopy or surgery. Hepatic infarction (HI) was defined as lower density area of the liver on enhanced CT images within postoperative day 7 with abnormal liver function tests. Surgical site infections included surgical wounds or intra-abdominal abscesses with positive cultures. Intra-abdominal abscess including liver abscess was defined as intra-abdominal fluid collection with positive cultures identified by ultrasonography or computed tomography associated with

persistent fever and elevation of the white blood cell count. Mortality was defined as in-hospital death from any cause.

Statistical analysis

Statistical comparison between the two groups was made using the chi-square statistic, Fisher's exact test, or the Mann-Whitney *U* test, where appropriate. Baseline characteristics, operative outcomes, and postoperative complications were compared between the patients with and without IG by means of the chi-square test for continuous and categorical variables. Univariate analyses (chi-square test or the Kaplan–Meier method) were primarily used for selecting variables on the basis of a *p* value < 0.05. Significant variables and clinically effective factors were subjected to forward logistic regression analysis to determine net effect for each predictor while controlling the effects of the other factors. Odds ratios (ORs) and their 95% confidential intervals (CIs) were used to assess independent contributions of significant factors. Data were expressed as median. The cutoff value for the identified parameter (creatinine kinase [CK], lactate dehydrogenase [LDH]) was determined to maximize the difference between the cases with and without IG by receiver operating characteristic (ROC) curve. The relationship between the two groups divided by the cutoff value was analyzed by chi-square test for categorical variables. Cumulative overall survival was calculated by Kaplan–Meier method, and a comparison of the survival curves was analyzed using the log-rank test. All survival times were evaluated from the operative day. Statistically significant difference was considered to be *p* < 0.05. All analyses were performed using the statistical software package SPSS II (version 20.0; SPSS, Inc., Chicago, IL).

Results

Patient characteristics

Table 1 shows the characteristics of the 50 consecutive patients with pancreatic body/tail carcinoma. Combined resection of the portal venous system was performed for 13 patients (26%). Of the 50 patients, 26 received preoperative therapy (14 with chemotherapy, 11 with chemoradiotherapy) and the remaining 24 patients underwent upfront surgery. Regional lymph node metastases developed in 31 patients (62%). For one patient, a minute peritoneal nodule at the mesenterium of the small intestine found in closing the abdomen proved to be an M1 lesion and was diagnosed as stage 4 disease. R0 resection was achieved in 31 patients (62%), whereas R1/2 resection was found in 19 patients (38%); at the pancreatic cut end margin in one patient, retroperitoneal dissected tissue in 18 patients. The positive margin resection rate declined from 58% in the upfront strategy period to 19% in the period of neoadjuvant therapy strategy ($P = 0.005$).

Surgical outcome

Surgical outcomes including the incidence of operative morbidity, mortality, and the completion of postoperative adjuvant chemotherapy are shown in Table 2. Major complications of higher than grade 3 were observed in 21 patients (42%). Mortality rate was 8%. Three (75%) reoperation cases ($n = 4$) were associated with ischemia-related complications (total gastrectomy, $n = 2$; cholecystectomy, $n = 1$), and the other one (25%) was performed due to the impossibility of hemostasis with interventional radiology (IVR), each reflecting DP-CAR-specific issue complications. Twenty-eight (56%) patients completed the planned adjuvant chemotherapy of more than 60% dose intensity (Table 2).

Operative mortality

Regarding operative mortality, the first patient died of rapidly progressed peritoneal dissemination from residual cancer on day 51. The second patient died of uncontrollable hemorrhage from the portal vein without pancreatic fistula on day 28. The third patient died of multiple organ failure from clinically relevant pancreatic fistula which leads to post-pancreatectomy hemorrhage from the pseudoaneurysm located on the CHA stump on day 50. The last patient died of severe cardiac failure following acute myocardial infarction the previous day, 11 days postoperatively.

Ischemic gastropathy

Refractory gastroduodenal ulcer was seen in two patients and necrotic change of the gastric wall in three patients.

Table 2 Surgical outcomes of distal pancreatectomy with en bloc celiac axis resection ($n = 50$)

Morbidity	23 (46%)
Clavien-Dindo classification	
Grade 0–II	29 (58%)
Grade IIIa	15 (30%)
Grade IIIb	2 (4%)
Grade IV	0
Mortality (grade V)	4 (8%)
Pancreatic fistula ^a	14 (28%)
Grade A	1 (2%)
Grade B	10 (20%)
Grade C	3 (6%)
Delayed gastric emptying ^b	16 (32%)
Grade A	7 (14%)
Grade B	4 (8%)
Grade C	5 (10%)
Ischemic gastropathy	5 (10%)
Intra-abdominal hemorrhage	7 (14%)
Hepatic infarction	
Partial (< 3 segments)	17 (34%)
Broad (≥ 3 segments)	11 (22%)
Liver abscess	3 (6%)
Postoperative hospital stay, days	21 (10–192)
Readmission	7 (14%)
Completion of planned postoperative adjuvant therapy	28 (56%)

DP-CAR distal pancreatectomy with en bloc celiac axis resection, CT computed tomography, *nc* not calculated

^a Values are median (range) or number (percentage), unless otherwise stated

^b Pancreatic fistula and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgeons

Univariate analysis was also performed for the risk factors of IG (Table 3). To calculate the cutoff value of postoperative peak CK/LDH for prediction of discrimination between patients with and without IG, we employed ROC analysis in this study. The areas under the curve (AUC) for cutoff value were 0.893 (95% confidential interval = 0.779–1.000) for CK and 0.899 (95% confidential interval = 0.724–1.000) for LDH, respectively. The determined cutoff values to discriminate between patients with and without IG were 1005 IU/L for CK and 494 IU/L for LDH, respectively. Although LGA resection ($P = 0.046$), combined left IPA and LGA resection ($P = 0.012$), and $CK \geq$ cutoff value of IG ($P = 0.025$) were significant risk factors for IG, these variables were not in the equation logistic regression in the multivariate analysis because all these factors were positive in patients who presented IG. Therefore, multivariate logistic regression analysis could not be demonstrated in the study.

Table 3 Univariate analysis about the risk factors/outcomes of ischemic gastropathy ($n = 50$)

Factor/outcome		Univariate analysis		
		IG (-) ($n = 45$)	IG (+) ($n = 5$)	<i>P</i> value
Age, years	≥ 68	22	3	0.500
	< 68	23	2	
Sex	Man	27	5	0.095
	Woman	18	0	
ASA	≥ 3	8	1	0.646
	< 3	37	4	
BMI (kg/m ²)	≥ 25	7	2	0.216
	< 25	38	3	
Neoadjuvant therapy	Yes	21	4	0.174
	No	24	1	
Operative time (min)	≥ 340	22	4	0.200
	< 340	23	1	
Blood loss (mL)	≥ 500	21	4	0.174
	< 500	24	1	
Portal vein resection	Yes	11	2	0.389
	No	34	3	
Pancreatic fistula (grade B, C) ^a	Yes	11	2	0.389
	No	34	3	
T4 (celiac axis invasion)	Yes	6	0	0.513
	No	39	5	
LGA resection	Yes	23	5	0.046*
	No	22	0	
Both left IPA/LGA resection	Yes	17	5	0.012*
	No	28	0	
CK	≥ 1005 IU/L ^b	20	5	0.025*
	< 1005 IU/L	25	0	
LDH	≥ 494 IU/L ^b	21	4	0.174
	< 494 IU/L	24	1	

IG ischemic gastropathy, ASA-PS American Society of Anesthesiologists-Physical Status, BMI body mass index, IPA inferior phrenic artery, LGA left gastric artery, IPA inferior phrenic artery, CK creatine kinase, LDH lactate dehydrogenase, IG ischemic gastropathy, *nc* not calculated

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

^b Cutoff values of IG were determined by ROC curve

Survival

Median follow-up time was 16 (0–125) months. The estimated 1-, 2-, and 5-year survival rates were 66, 36, and 8%, respectively, and estimated median survival time (MST) was 16 months in all patients, including four cases of mortality. Estimated recurrence-free survival time (RFS) was 8 (2–122) months. Regarding comparison of estimated overall survival (OS) and RFS of conventional DP-CAR and modified DP-CAR, there was no significant difference between the two groups ($P = 0.101$ and $P = 0.827$, respectively, log-rank test). According to the local recurrence rate excluding the mortality cases, there was no significant difference between the two groups ($P = 0.182$). Table 4 shows the univariate and multivariate logistic regression analysis of prognostic factors. Among these clinicopathologic prognostic factors, independent predictors of prognosis even after control for the other

variables were IG (OR, 5.997; 95% CI, 1.543–23.309; $P = 0.010$), the completion of planned adjuvant chemotherapy (OR, 0.282; 95% CI, 0.121–0.654; $P = 0.003$), operative time (OR, 2.261; 95% CI, 1.084–4.714; $P = 0.030$), and age (OR, 2.212; 95% CI, 1.081–4.524; $P = 0.030$). All patients with IG had tumor invasion to both of LGA and left IPA, required longer median operative time of 471 min (233–846), and failed to complete adjuvant chemotherapy. In addition, the estimated overall survival rate in patients with IG ($n = 5$) was lower than that of the other patients ($n = 45$) ($P < 0.001$, log-rank test) (Fig. 4).

Postoperative nutritional status

There were no differences in preoperative nutritional data between patients who underwent conventional DP-CAR and modified DP-CAR, including the values of TP (7.20 ± 0.54

Table 4 Univariate and multivariate analyses of prognostic risk factors

Variable		Univariate analysis		Multivariate analysis		
		MST (days)	<i>P</i> value	OR	95% CI	<i>P</i> value
Age	≥ 68/< 68	481/647	0.029 ^a	2.212	1.081–4.524	0.030 ^a
Sex	Male/female	647/435	0.787			
ASA-PS	≥ 3/< 3	457/526	0.988			
BMI (kg/m ²)	≥ 25/< 25	384/526	0.033 ^a	1.229	0.493–3.061	0.659
Neoadjuvant therapy	Yes/no	481/646	0.333			
Operative time (min)	≥ 340/< 340	421/747	0.017 ^a	2.261	1.084–4.714	0.030 ^a
Blood loss (mL)	≥ 500/< 500	647/500	0.772			
Blood transfusion	Yes/no	384/647	0.122			
Primary tumor	T4/T1–3	761/500	0.591			
Portal vein resection	Yes/no	290/647	0.242			
LGA resection	Yes/no	457/646	0.114			
Both left IPA/LGA resection	Yes/no	379/646	0.159			
Pancreatic fistula (grade B, C) ^a	Yes/no	421/647	0.114			
DGE (grade B, C) ^a	Yes/no	234/647	0.004 ^a	0.820	0.247–2.721	0.746
Ischemic gastropathy	Yes/no	51/647	<0.001 ^a	5.997	1.543–23.309	0.010 ^a
Hepatic infarction	Yes/no	421/650	0.194			
Liver abscess	Yes/no	500/526	0.558			
Number of positive lymph node metastasis	≥ 4/< 4	457/647	0.035 ^a	2.248	0.935–5.405	0.070
Residual tumor status	R0/R1, 2	435/646	0.201			
Histopathologic type	Poor/other	781/500	0.261			
Arterial invasion	Yes/no	481/500	0.123			
Portal venous invasion	Yes/no	475/646	0.303			
Extrapancreatic perineural invasion	Yes/no	526/500	0.334			
Completion of adjuvant therapy	Yes/no	781/240	0.001 ^a	0.282	0.121–0.654	0.003 ^a

ASA-PS American Society of Anesthesiologists-Physical Status, BMI body mass index, LGA left gastric artery, IPA inferior phrenic artery, DGE delayed gastric emptying, MST, median survival time, OR odds ratios, CI confidential interval

^a Pancreatic fistula and delayed gastric emptying were defined according to the International Study Group of Pancreatic Surgeons

vs 7.18 ± 0.64 g/dl, $P = 0.899$), Alb (4.24 ± 0.25 vs 4.21 ± 0.41 g/dl, $P = 0.791$), and TC (177.3 ± 23.9 vs 187.5 ± 37.0 mg/dl, $P = 0.319$). Postoperative values were significantly higher in patients who underwent modified DP-CAR than those with conventional DP-CAR in TP (7.17 ± 0.56 vs 6.65 ± 0.66 g/dl, $P = 0.007$), Alb (4.04 ± 0.45 vs 3.43 ± 0.43 g/dl, $P < 0.001$), and TC (162.3 ± 34.7 vs 141.6 ± 27.2 mg/dl, $P = 0.044$). There were no differences, however, in body weight loss between the two groups (-7.03 ± 3.8 vs -5.40 ± 3.0 kg, $P = 0.127$).

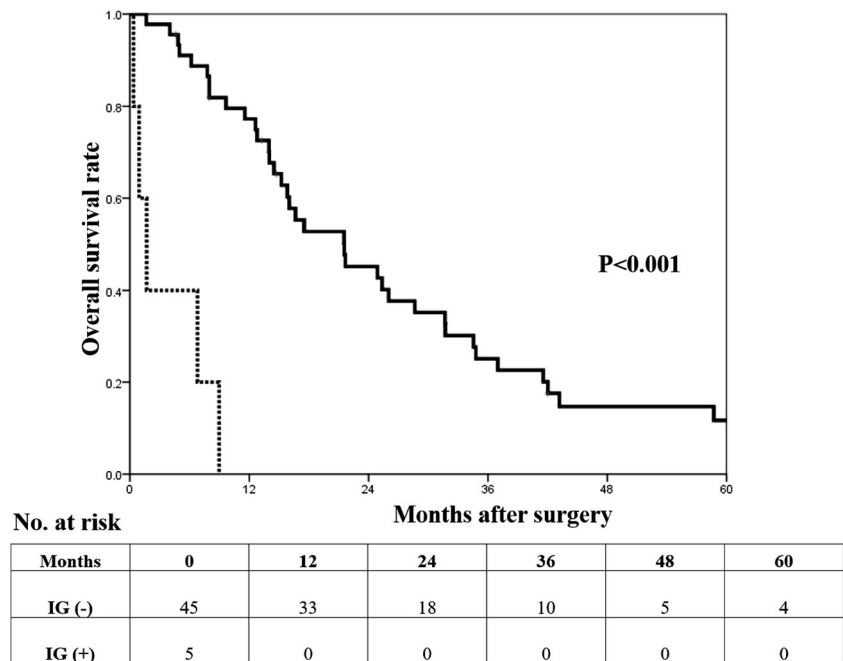
Discussion

In the present study, we investigated the risk factors for IG and the prognostic factors for survival by analyzing clinicopathological data including ischemic complications in patients who underwent DP-CAR. Both left IPA and LGA resection and CK \geq cutoff value of IG were significant risk factors for IG,

and IG remained an independent prognostic predictor of the mortality or early recurrence. This result might be interpreted as the significance of LGA reconstruction especially in the cases with resection of combined left IPA and LGA after DP-CAR [29, 30], and an elevated CK value ≥ 1005 IU/L was associated with IG. CK is an abundantly present enzyme in skeletal, cardiac, and smooth muscles. If muscle necrosis occurs in an organ, CK appears in the bloodstream and serum concentration level is elevated. The predictive ability of CK is controversial for intestinal ischemia [31, 32], but the significance of peak CK level for organ necrosis depends on the type of organ [33] or the muscle mass volume of each organ. CK was revealed as an independent risk factor for IG in the present study, possibly reflecting more muscle mass in the stomach than in the intestine.

Next, we investigated the nutritional data in two DP-CAR groups. There were no differences in loss of body weight between the two groups, but they have better nutrition in patients who underwent modified DP-CAR than those who

Fig. 4 Comparison of overall survival curves according to the occurrence of ischemic gastropathy (IG). Overall survival rate was significantly lower in patients with IG (dotted line, $n = 5$) compared to those without IG (solid line, $n = 45$) (log-rank test)



underwent conventional DP-CAR. Taken together, modified DP-CAR could have indirectly improved the completion rate of adjuvant therapy by decreasing the incidence of IG and preventing postoperative nutritional deterioration. Currently, we perform LGA reconstruction by middle colic artery-left gastric artery (MCA-LGA) bypass after conventional DP-CAR [30], and a direct bypass from the aorta to the LGA could be another reconstruction option.

On investigation of prognostic risk factors, completion of planned adjuvant chemotherapy remained a significant predictor of favorable prognosis. This might be a universal result as similarly demonstrated in large scale prospective studies [2]. In this context, we had expected that preserving the LGA in modified DP-CAR directly improved survival time by decreasing the incidence of IG. There was no significant survival benefit in modified DP-CAR, however, compared with conventional DP-CAR. It could be due to the oncologic characteristic of tumor-involving arteries tending to recur systemically and rapidly even after radical resection.

In contrast, the incidence of morbidity and mortality was high in patients who underwent DP-CAR compared with several other series [12, 34] and impacting on the overall survival rate. All morbidity requiring reoperation was directly caused by DP-CAR-specific complications, and most mortality indirectly associated with intra-abdominal hemorrhage from the DP-CAR-specific arterial stump, which is extremely difficult to rescue by IVR. Thus, DP-CAR is still a developing surgery, which should be modified for safely against ischemia-related complications, and risk factors for post-pancreatectomy hemorrhages such as pancreatic fistula should be reduced. Contrary to previous reports, indications for DP-CAR remain

controversial with regard to the curability, survival benefit, and high mortality rate. In this study, pathologically positive invasion of CA was only 12%. It remains debatable whether DP-CAR was really beneficial for all tumors involving CA. However, the microscopically positive margins were detected more frequently in patients with tumors situated near the origin of SA in previous study [9]. We therefore believe that DP-CAR is one surgical option to obtain R0 resection for the clinical T4 pancreatic body tumors. In the landmark era of a safer Appleby operation and introduction of stronger regimens of chemotherapy for borderline resectable or locally advanced pancreatic carcinoma [3, 35], pancreatic surgeons will return to this procedure again as a radical pancreatectomy. The procedure may be justified in strictly selected patients owing to the potential survival benefits as there will be increased chances to evaluate indication of DP-CAR.

Our results may be limited by being from a single institution and the retrospective nature of the study. More importantly, the outcome occurs over a very long period of time, and the patients and their treatments, both surgical and chemotherapeutic, evolve over time. The high degree of well-moderate differentiated cancer is typically reported in Asia but comparatively less common in other populations. This may have an effect on the reported response of chemotherapy [36, 37].

In conclusion, the poorer prognosis in patients who undergo DP-CAR may be related to more advanced tumors. Combined left IPA and LGA resection was a significant risk factor for IG. Among clinicopathologic prognostic factors, IG remains an independent predictor of prognosis in patients who undergo DP-CAR.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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