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Ischemic gastropathy after distal pancreatectomy with en bloc celiac axis resection versus distal pancreatectomy for pancreatic body/tail cancer☆,☆☆

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ABSTRACT

Background: Ischemic gastropathy (IG) is a major complication after distal pancreatectomy with en bloc celiac axis resection (DP-CAR) for locally advanced body/tail pancreatic ductal adenocarcinoma (PDAC), and its incidence is still unknown.
Methods: To evaluate the occurrence of IG, 77 and 18 consecutive patients with body/tail PDAC were analyzed in a retrospective and a prospective study, respectively. We utilized perioperative gastroendoscopy, Gastrointestinal Quality of Life Index (GIQLI) score, and quantitative assessment for gastric arterial blood flow using the HyperEye Medical System (HEMS) with indocyanine green (ICG) fluorescence imaging in the prospective arm.
Results: In the retrospective arm, no significant difference was noted in the occurrence rate of IG between the DP-CAR (8.7%) and DP groups (5.5%). In the prospective arm, the postoperative endoscopic scores were significantly higher in the DP-CAR group (45%) than in the DP group (11%) ($p < .0007$) despite no difference in the GIQLI score. The ICG-HEMS imaging system demonstrated more delayed arterial flow velocity in the IG (+) group ($p < .028$), but showed no significant difference in arterial flow volume compared to the IG (−) group.
Conclusion: This is the first demonstration assessing IG incidence after DP-CAR using multiple methods. Despite the high IG rate, gastric arterial flow volume was almost equally maintained in DP-CAR patients with or without IG compared with the DP group. We should note the fact that many of the IG patients do not present with typical symptoms, and proper treatment is required for those "silent" IG patients.

Introduction

Distal pancreatectomy (DP) with en bloc celiac axis resection (DP-CAR) is a radical operation proposed for locally advanced body pancreatic ductal adenocarcinoma (PDAC), which involves the celiac axis (CA) or common hepatic artery (CHA) and spreads toward the celiac plexus and ganglia directly or perineurally via the nerve plexus [1]. After the concomitant resection of the CA, CHA, and left gastric artery (LGA) in DP-CAR, collateral pathways via the superior mesenteric artery (SMA), pancreaticoduodenal arcades, and gastroduodenal artery maintain the arterial blood supply to the hepatobiliary system. Since the collateral pathways also ensure arterial flow to the right gastroepiploic artery, the whole stomach can be preserved unless the tumor involves the stomach.

The higher occurrence rate of postoperative ischemic complications after DP-CAR than after DP is an issue. The CA and CHA resection in DP-CAR could cause liver abscess due to the lack of hepatic blood flow. However, the incidence of postoperative hepatic or gallbladder necrosis after DP-CAR is rare because of collateral flow to the hepatobiliary system. In contrast, ischemic gastropathy (IG) is a major complication in DP-CAR, which appears as gastric/duodenal ulcers or perforation in the postoperative state.

Kondo et al. reported that gastric ulceration occurred in 33% of postoperative patients after DP-CAR, and preoperative coil embolization of the CHA and LGA may prevent postoperative IG by stimulating the development of collateral pathways from the SMA to the stomach [2,3].

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The occurrence rate of IG after DP-CAR decreased dramatically to 13% after preoperative coil embolization [4]. Meanwhile, a case of duodenal perforation, presumably from ischemia after DP-CAR, was reported although preoperative coil embolization of CHA and LGA was performed prior to DP-CAR [5]. Recently, in a pan-European study, Klompmaker et al. reported that 3 of 68 patients (4.4%) required reoperation (gastric wedge resection) due to the ischemia of the stomach after DP-CAR [6]. No previous prospective study has been reported to evaluate the occurrence of ischemia-related gastric complications associated with DP-CAR.

This study focused on the complications associated with IG in patients who underwent DP-CAR compared to those who underwent DP. To the best of our knowledge, this is the first demonstration of a prospective study evaluating IG using preoperative and postoperative endoscopic examination, a questionnaire, and an intraoperative visible method for the measurement of gastric blood flow. These findings will provide a new insight to manage the postoperative IG of PDAC patients undergoing DP-CAR.

Material and methods

Of the 95 consecutive patients with body/tail PDAC, 77 (DP-CAR: 23, DP: 54) patients were included in the retrospective study between February 2004 and August 2014 (Table 1), and 18 (DP-CAR: 9, DP: 9) patients were also included in the prospective study between October 2014 and September 2015 (Table 2) in the Department of General Surgery at Chiba University Hospital (Fig. 1). Patients older than 20 years of age, and tumors were diagnosed as PDAC histologically. The duration of patients' enrollment of the prospective study was planned for 1 year. DP-CAR was performed for pancreatic tumors invading or contacting the CHA, CA, or splenic artery (SPA) along with en bloc resection of the CHA, CA, LGA, celiac plexus and ganglions with regional lymph node resection. Among all 23 DP-CAR cases in the retrospective arm, 17 patients (74%) underwent preoperative coil embolization of the CHA. The LGA and CHA were embolized to enlarge the collateral pathways to the stomach and prevent IG in 12 out of 17 patients. In the prospective arm, preoperative coil embolization of the CHA and LGA was performed in all 9 DP-CAR cases. These studies were performed in accordance with the precepts of the Declaration of Helsinki and approved by the research ethics committee of the graduate school of medicine, Chiba University (the numbers of ethical approval are #1852 and #2732). The study design of the prospective arm was also approved by the local ethics committee, UMIN Clinical Trials Registry (registration number: UMIN000033977). Written informed consent was obtained from all patients.

Table 1
Clinical parameters of participants in the retrospective study.

Perioperative clinical parameters	DP-CAR (N = 23)	DP (N = 54)	*p* value
Age (years)	62.0 ± 8.6	67.5 ± 7.7	.99
Gender (M/F)	15 / 8	33 / 21	.73
Neoadjuvant chemotherapy	18 (78%)	4 (7.2%)	*< .001**
Preoperative CA19–9 (U/ml)	232 ± 641	150 ± 1272	.74
Operation time (min)	294 ± 90	246 ± 96	*.016**
Blood loss volume (g)	1270 ± 2012	648 ± 1188	*.036**
Concomitant resection			
Portal vein	11 (48%)	6 (11%)	*.0003**
Stomach	2 (8.6%)	5 (9.2%)	.93
Transverse colon	1 (4.3%)	5 (9.2%)	.46
Postoperative complication (C-D ≧ IIIa)	16 (69.5%)	25 (46.3%)	.061
Ischemic gastropathy (IG)	**2 (8.7%)**	**3 (5.5%)**	**.61**
Delayed gastric emptying (grade B, C)	4 (17.4%)	9 (16.6%)	.94
Pancreatic fistula (grade B, C)	10 (43.4%)	22 (40.7%)	.82
Restart of oral intake (POD)	3.5 ± 8.2	4.5 ± 3.2	.68
Postoperative hospital stay (POD)	34.0 ± 34.9	24.0 ± 26.4	.071
the 90-day mortality	1 (4.3%)	0 (0%)	.12
Adjuvant Chemotherapy	19 (83%)	51 (93%)	.098
Start of adjuvant chemotherapy (POD)	49.0 ± 26.7	49.5 ± 148.3	.77

* : significant value. N: the total number of admissions in that category. Absolute numbers shown with percentages in brackets. C-D: Clavien-Dindo classification. POD: postoperative day.

Table 2
Clinical parameters of participants in the prospective study.

Perioperative clinical parameters	DP-CAR (N = 9)	DP (N = 9)	*p* value
Age (years)	61.0 ± 14.2	72.0 ± 4.0	.98
Gender (M/F)	7 / 2	5 / 4	.73
Neoadjuvant therapy	9 (100%)	1 (11.1%)	*< .001**
Operation time (min)	369 ± 89	255 ± 65	*.0057**
Blood loss volume (g)	920 ± 1675	755 ± 328	.068
Concomitant resection			
Portal vein	6 (66.7%)	0	*.0027**
Stomach	2 (22.2%)	1 (11.1%)	.53
Postoperative complication (C-D ≧ IIIa)	6 (66.7%)	7 (77.7%)	.061
Ischemic gastropathy (IG)	**4 (44.4%)**	**1 (11.1%)**	**.11**
Delayed gastric emptying (grade B, C)	2 (22.2%)	1 (11.1%)	.53
Pancreatic fistula (grade B, C)	5 (55.5%)	5 (55.5%)	1.00
Restart of oral intake (POD)	3.0 ± 1.6	2.0 ± 0.4	*.0025**
Postoperative hospital stay (POD)	40.0 ± 18.7	27.0 ± 27.7	.44
the 90-day mortality	0	0	—
Adjuvant Chemotherapy	6 (66.7%)	8 (88.9%)	.098
Start of adjuvant chemotherapy (POD)	54.0 ± 115.1	58.0 ± 33.4	.25

* : significant value. N: the total number of admissions in that category. Absolute numbers shown with percentages in brackets. C-D: Clavien-Dindo classification. POD: postoperative day.

Gastrointestinal endoscopy was performed before and a week after the operation in the prospective arm to assess the patients' stomach condition. We examined the endoscopic findings of the patients according to the scoring system that we made for objective assessment, including ischemic change, as shown in Supplemental Table 1. All IGs were assessed by gastrointestinal endoscopy in these two studies. A patient who had ulcerations was defined as an IG patient, and all patients were categorized into the IG (+) and IG (−) group.

Gastrointestinal Quality of Life Index (GIQLI) is a scoring system used to assess health-related quality of life in clinical studies of patients with gastrointestinal diseases [7]. Briefly, the GIQLI score is calculated from the patients' answers to a questionnaire containing 36 questions each with 5 response categories, which examines the symptoms and physical, emotional, and social dysfunction related to the gastrointestinal diseases or their treatments. The score of each question varies from 0 to 4 points, and the most desirable option gets 4 points. Thus, a high score means high gastrointestinal quality of life of the patient. The participants of our study answered the same GIQLI questionnaire twice, before and 7 days after the surgery.

To evaluate the gastric blood flow before and after resection of the major arteries, the HyperEye Medical System (HEMS: Mizuho Medical Co. Ltd., Tokyo, Japan) was applied to visualize indocyanine green (ICG)-enhanced structures with vivid color [8]. The measurements were performed twice in each operation, the first measurement was made just after the laparotomy (referred to as "PRE"), and the second was done after resection of the pancreas and major arteries (referred to as "POST"). We routinely checked the systolic arterial blood pressure at the time of measurement to keep it within the ideal range (80–110 mmHg). Fluorescence intensities (FIs) were measured in arbitrary intensity units corresponding to the intensity. The data of the ICG measurements were analyzed for quantitative assessment using the Japan luminance-analyzing software (Mizuho Medical Co. Ltd., Tokyo, Japan). The course of FIs could be measured in freely definable regions of interest (ROIs). We set 4 ROIs (each ROI is a 1 cm circular diameter) to measure and analyze the luminance of ICG fluorescence in the stomach: (1) the lesser and (2) greater curvature of the gastric body, (3) upper gastric body, and (4) pyloric zone, using the HEMS software. We also measured the negative control intensity (NCI) in the field outside of the intra-abdominal space and the positive control intensity (PCI) in the syringe filled with diluted ICG (0.025 mg/mL), which shows high FI due to the quenching phenomena. For quantitative

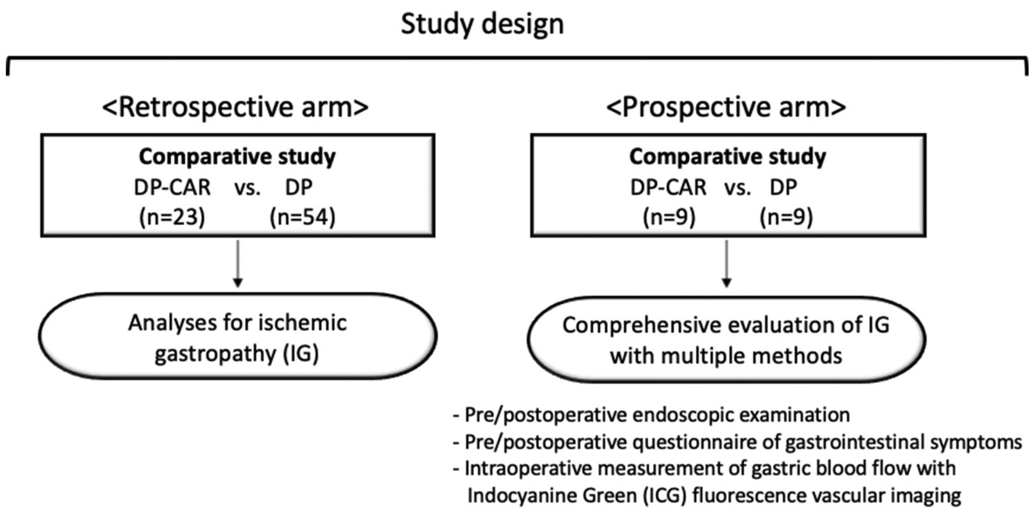

Fig. 1. Schema of the study design.

assessment of FIs in the stomach, we set the parameter "blood flow intensity (BFI)" which was calculated as BFI = (FI - NCI) / (PCI - NCI). We constructed the time-BFI curve and assessed the following parameters: "Δmaximum BFI" as determined from the exported fluorescence curves; "climbing time", i.e., the time interval between the initial appearance of fluorescence within the field of view and the maximum BFI; and "climbing gradient", i.e., Δmaximum BFI/climbing time. We performed a comparative analysis of PRE and POST repeated measured data in the same patients.

Data were expressed as median ± standard deviation. Statistical analyses were performed using the Mann–Whitney–Wilcoxon test and Welch's *t*-test for continuous data and the Chi-square test for categorical data. $P < .05$ was considered statistically significant.

Results

Comparisons of clinical variables between DP-CAR group and DP group in the retrospective study

In the retrospective arm, the median operation time ($p = .016$) was significantly longer and median blood loss volume ($p = .036$) was also higher in the DP-CAR group than in the DP group (Table 1). No complication associated with preoperative coiling of CHA and LGA was observed in any of the DP-CAR patients. Despite of no significant difference in the occurrence rate of IG between DP-CAR group and DP group, especially, 2 patients after DP-CAR developed severe IG complication. One patient had gastric perforation at 5 days after DP-CAR with gastric partial resection, and the other patient had severe gastritis with strong mucosal edema of the stomach, and needed a long recovery period. Furthermore, 6 of 23 (26.1%) DP-CAR patients and 5 of 54 (9.3%) DP patients needed more than 10 days to restart their oral intake. These results suggested that IG is one of the most considerable complications in patients with the body/tail PDAC after pancreatectomy.

Comparisons of clinical variables between DP-CAR group and DP group in the prospective study

In the prospective arm, the operation time was significantly longer ($p = .0057$), and no complication occurred after preoperative coiling of CHA and LGA in the DP-CAR group as well as in the retrospective arm. Notably, the postoperative date to restart oral intake was significantly late in DP-CAR patients compared to the DP patients in the prospective arm ($p = .0025$) (Table 2). In particular, 2 patients in the prospective arm were forced to fast after DP-CAR for over 1 week in order to recover the condition of the stomach. Central venous nutrition was used for them to supply the calories instead of oral intake.

Evaluation and comparisons of the occurrence of IG patients by gastrointestinal endoscopy

To evaluate the occurrence of IG after the operation, we first performed gastrointestinal endoscopy. Based on the scores of the endoscopic findings (Supplemental Table 1), no significant difference was noted in the preoperative endoscopic scores between the DP-CAR and DP groups. The postoperative endoscopic findings indicated erosive, hemorrhagic, and edematous mucosa with multiple ulcerations as shown in Fig. 2. The score after the operation was significantly higher in the DP-CAR group compared to the DP group ($p < .0007$) (Table 3). Gastric ulcerations were observed in 4 patients (45%) in the DP-CAR group and in 1 patient (11%) in the DP group, and these 5 patients were defined as postoperative IG cases.

Questionnaire for clinical gastrointestinal symptoms using GIQLI score

Next, we analyzed postoperative IG using the GIQLI questionnaire. Most patients had poor GIQLI score after the operation; however, there was no significant difference in the GIQLI score before and after the operation between the DP-CAR and DP groups (Supplemental Table 2). Likewise, there was no significant difference in the GIQLI score between the patients with and without IG in the DP-CAR group (Table 4). Therefore, these results suggested that it is difficult to estimate the occurrence of IG after DP-CAR using a questionnaire.

Quantitative analyses for intraoperative gastric arterial blood flow using the ICG-HEMS imaging system

The ICG-HEMS imaging system was utilized to analyze whether the change in the intraoperative method for the measurement of gastric blood flow affects the incidence of IG after surgery. The representative figures for the first measurement (PRE), second measurement (POST), and 4 ROIs for measurement are shown in Fig. 3a. Three parameters were analyzed as follows: (i) "climbing time", which is considered to be the main duration of arterial flow in the stomach wall, (ii) "Δmaximum BFI", which stands for arterial flow volume, and (iii) "climbing gradient", which represents arterial flow velocity (Fig. 3b). Comparing the climbing gradient at all 4 points in both PRE and POST measurement, the level of POST climbing gradient in the lesser curvature of the gastric body was significantly lower than the PRE measurement in DP-CAR ($p < .043$) but not in DP (Fig. 3c). However, the

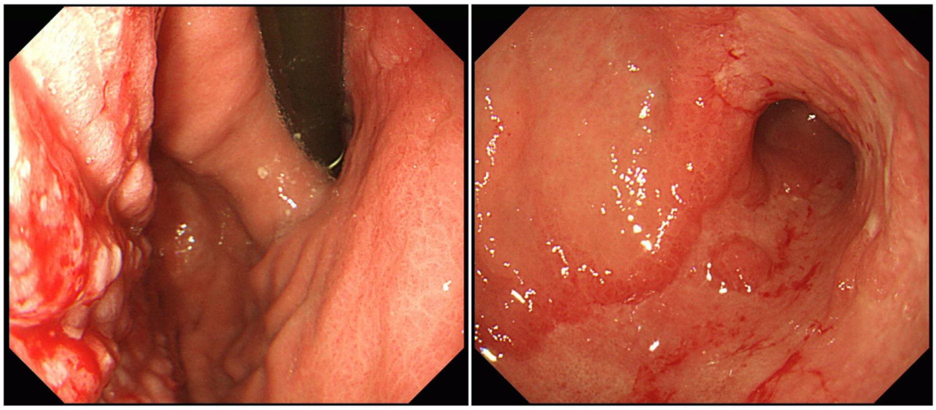

Fig. 2. Representative endoscopic findings of ischemic gastropathy Endoscopic findings of the stomach at 7 days after distal pancreatectomy with en bloc celiac axis resection. Left panel: Edematous mucosa with oozing blood covers a large area in the greater curvature of the upper gastric body. Right panel: Multiple, irregular, and shallow ulcers are found in the lesser and greater curvature of the gastric body.

change rate of the climbing gradient from PRE to POST measurement did not show significant differences at any points between both groups. Furthermore, no significant difference was noted in the climbing gradient level at any points between the IG (−) and IG (+) in the DP-CAR group, while the POST climbing gradient level was significantly lower than the PRE climbing gradient level in the upper gastric body in the IG (+) group ($p < 0.028$) but not in the IG (−) group (Fig. 3d). These results indicated that the ICG-HEMS imaging system demonstrated delayed arterial flow velocity, but showed no significant differences in arterial flow volume in the stomach in the IG (+) group.

Discussion

In this study, we analyzed the postoperative IG of PDAC patients who underwent DP-CAR and DP using several objective methods. Our study demonstrated the possibility of quantitative measurement for gastric blood flow using ICG luminance and that the occurrence of IG after DP-CAR is higher than expected. Based on the anatomical findings, insufficient blood perfusion in the stomach induced after DP-CAR is considered particularly in the area from the upper gastric body to the lesser curvature. Preservation of the right gastric/gastroepiploic artery/vein and maintenance of the intramural capillary network of the stomach seem to be important in maintaining sufficient blood perfusion in the stomach. The right gastric artery and vein were routinely preserved, whereas the right gastroepiploic artery and vein were sacrificed in 2 of 9 patients, and the left gastric vein was sacrificed in all 9 patients of the DP-CAR group in the prospective study. However, there was no correlation between these arteries and venous resection and IG rate in this prospective study (Supplemental Table 3). Additionally, there was also no correlation between the preservation of left inferior phrenic artery and the occurrence of IG in the prospective cohort (Supplemental Table 3). Despite of no correlation among these events, we have experienced that a patient had gastric perforation after DP-CAR with gastric partial resection in the retrospective arm, and a patient had IG after DP with gastric partial resection in the prospective arm. Thus, concomitant gastric resection caused by direct invasion to the stomach could be a major risk to ruin this intramural capillary network. Neoadjuvant chemotherapy and radiotherapy might influence on the condition of the stomach, especially in terms of the venous outflow. In the prospective arm, all 9 PDAC patients after DP-CAR received neoadjuvant chemotherapy (6 gemcitabine plus S-1: GS therapy, 2 gemcitabine plus nab-paclitaxel: GnP therapy, and 1 FOLFIRINOX and GnP therapy) or radiotherapy including carbon ion radiotherapy (CIRT). There is no correlation between the type of neoadjuvant chemotherapy and the occurrence of IG after DP-CAR (Supplemental Table 4). Interestingly, among 3 patients who received neoadjuvant radiotherapy, 2 of 2 patients who received CIRT and GS therapy prior to the surgery had IG. It is possible that radiation might impact the venous outflow to ruin the intramural capillary network.

This is the first study in which all DP-CAR and DP patients underwent endoscopic examinations to determine the precise occurrence rate of IG. We found that 4/9 cases (44%) in the DP-CAR group had postoperative IG with gastric ulcerations, and it was extremely higher than 8.7% of postoperative IG patients in the DP-CAR group of our retrospective cohort study and 12.9% in a previous report of systematic review and meta-analysis [9]. Indeed, Nakamura et al. recently reported a high incidence of IG (28.8%) in patients after DP-CAR [10]. Almost all DP-CAR patients showed various mucosal damages (redness, erosion, edema, and congestion) including those 4 cases with IG after DP-CAR. Thus, it is clearly shown that postoperative DP-CAR patients had a higher endoscopic score than DP patients. Importantly, some patients who developed IG did not complain of any particular digestive symptoms described in the questionnaire for GIQLI. These findings suggest that there are occult "silent" IG patients after DP-CAR. Actually, we did not perform the endoscopy until the patients complained of their epigastric distress in the retrospective cohort of study design 1. So, there might be the certain differences for the timing of gastroendoscopy between the retrospective and prospective arm. Additionally, these results implicate that a subset of patients with IG is possible to improve the stomach condition over time. The proton pump inhibitors were routinely administrated for all patients after DP-CAR in this study. Concerning the postoperative interventions, it might be worth performing postoperative endoscopy to assess the stomach condition precisely, and not only proton pump inhibitors but also gastric mucosa

Table 3
Comparisons of the endoscopic score between the DP-CAR group and the DP group.

	DP-CAR (N = 9)	DP (N = 9)	*p* value
Before operation	0.2 ± 0.4	0.2 ± 0.4	1.00
After operation	5.3 ± 1.2	2.9 ± 1.5	*.0007**
Change in endoscopic score	5.1 ± 1.4	2.7 ± 1.7	*.004**

Table 4
Comparison of the GIQLI score between the patients with and without ischemic gastropathy in the DP-CAR group.

	DP-CAR		*p* value
	IG (+) (N = 4)	IG (−) (N = 5)	
Before operation	111.7 ± 9.6	113.8 ± 22.9	.56
After operation	73.5 ± 14.8	92.8 ± 28.2	.85
Change in GIQLI point	−38.3 ± 22.7	−22.0 ± 41.7	.74

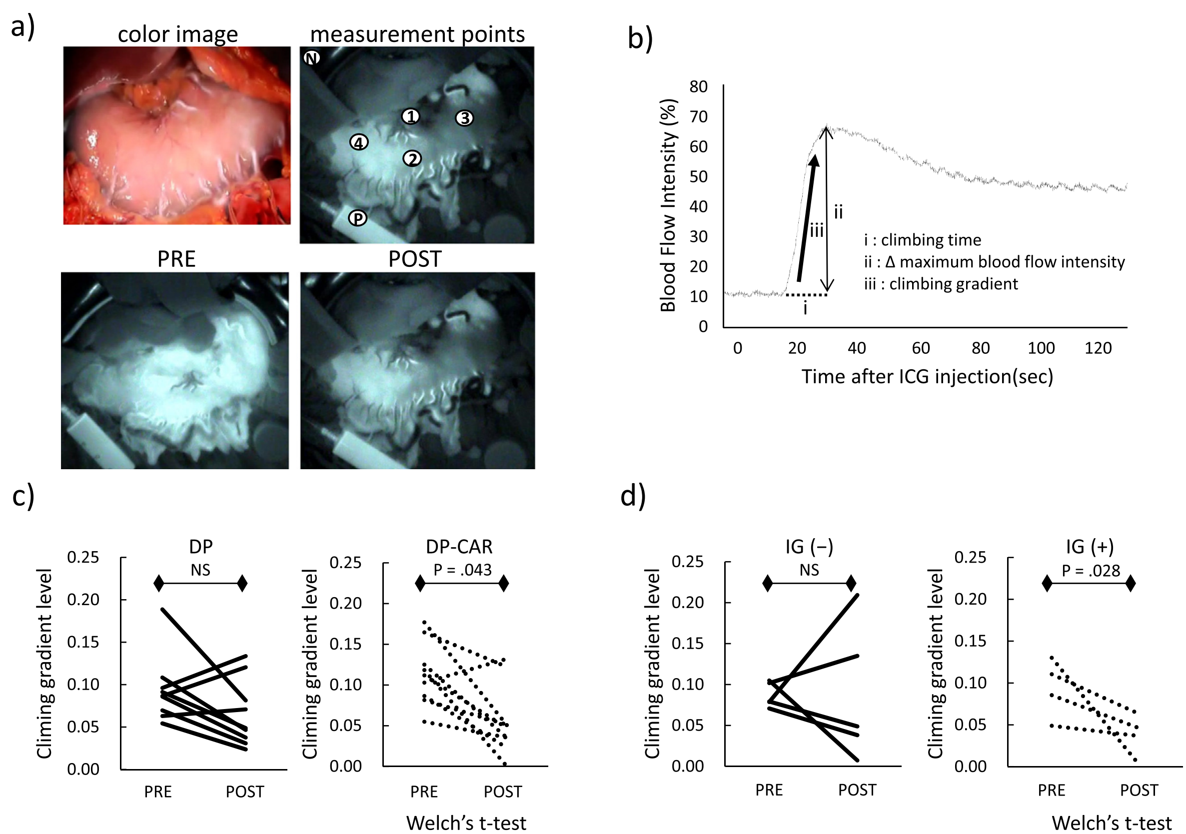

Fig. 3. Quantitative analyses using indocyanine green- HyperEye Medical System (ICG-HEMS) imaging a) Left panel: the first measurement (PRE) performed just after laparotomy. The perfusion of the whole gastric wall can be seen as indocyanine green (ICG) fluorescence. Middle panel: the second measurement (POST) after resection of the major arteries and pancreas show lower fluorescence intensity in the area of the upper gastric body and lesser curvature of the gastric body. Right panel: 4 regions of interest and control regions: (1) lesser and (2) greater curvature of the gastric body, (3) upper gastric body, and (4) pyloric zone. (N) Negative control intensity area on the field outside of the intra-abdominal space, and (P) positive control intensity area on the syringe filled with diluted ICG (.025 mg/mL) to analyze the luminance of ICG fluorescence using the HEMS software. b) Time-blood flow Intensity curve of ICG fluorescence imaging. i: climbing time, ii: Δmaximum blood flow intensity, iii: climbing gradient. c) Comparison of climbing gradient level between PRE and POST measurement in the lesser curvature of the gastric body. d) Comparison of climbing gradient level between PRE and POST measurement in the upper gastric body in the distal pancreatectomy with en bloc celiac axis resection group.

protective agents are needed to manage and control the postoperative condition of the stomach and prevent delayed oral intake after DP-CAR.

We attempted to visualize and quantitatively analyze the blood perfusion to the stomach with intraoperative real-time near-infrared fluorescence of ICG imaging using the HEMS system. This intraoperative ICG fluorescence imaging has been in use for a decade and allows non-quantitative visualization of arterial, capillary, and venous systems in various fields of surgeries. It has been in practical use for assessing graft blood flow in cardiovascular surgeries, visualizing the hepatic artery and portal vein in hepatic surgeries, detecting intestinal ischemia in surgeries for abdominal aortic aneurysms, and evaluating blood flow of the gastric tube in esophagectomies [11–16]. In contrast, Detter et al. reported that the intraoperative ICG angiography seemed not useful to evaluate the blood perfusion in the anastomosis site because it cannot provide multidirectional evaluation like X-ray angiography [17].

In this study, ICG FI showed delayed recovery of the intensity level to the baseline especially in the upper gastric body and lesser curvature of the gastric body at POST measurement than at PRE measurement in DP-CAR cases. This observation demonstrated slower velocity of arterial flow to those areas of the stomach after resection of the major arteries than before. However, the lesser curvature in the gastric body was well-perfused even after preoperative LGA embolization was performed prior to the surgery. Indeed, intraoperative gastric arterial perfusion at POST measurement was eventually equivalent between the DP-CAR and DP group as well as the IG (+) and IG (−) cases. The quantitative measurement using ICG-HEMS imaging is likely to be difficult to predict intraoperatively following postoperative IG after DP-CAR. Actually, this study has been primarily designed to assess not only the arterial, but also the venous perfusion in the stomach because venous congestion was assumed as one of the major factors causing IG after DP-CAR. Unfortunately, due to the technical limitation of the ICG fluorescence imaging, we were unable to detect the FI of the venous and lymph flow separately. Development of modalities and methods for intraoperative assessment is necessary to predict the incidence of IG in patients after DP-CAR.

Conclusion

We investigated the incidence of IG after DP-CAR using multiple assessment methods. The velocity of arterial gastric flow was slower in IG (+) cases of the DP-CAR group; however, intraoperative gastric arterial flow volume was almost equally maintained in DP-CAR patients with or without IG compared with the DP group. One of the critical limitations is that a limited number of patients in each group were analyzed in this prospective study, and this might have influenced to the results of the statistical analyses. We should be aware of the fact that many of the IG patients do not present with typical gastrointestinal symptoms, and proper treatment is required for those "silent" IG patients. Further investigation for long-term prognosis and quality of life of IG patients after DP-CAR is needed.

Author contribution

All authors have contributed substantially to the conception, data acquisition and analysis, drafting and critical revision of this work. All authors have given their final approval of this version for publication.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2019.04.004.

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