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Strategy of Pancreatectomies for Pancreatic Ductal Adenocarcinoma in Patients with a History of Gastrectomy

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Recently, the incidence of pancreatectomy for patients with a history of upper abdominal surgery has been increasing. The clinical courses of 307 patients who underwent the pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) were retrospectively reviewed to clarify the impact of a history of gastrectomy in patients undergoing a pancreatectomy for PDAC. Among 307 patients, 28 (9.1%) had a history of gastrectomy, while 279 did not. We compared the difference in clinical course and prognostic outcomes between the groups. In patients with a history of gastrectomy, the 5-year survival rate was 17.6%, which was relatively poorer than that of patients without it (33.4%, $P = 0.1329$). A multivariate analysis of factors associated with the overall survival rate identified the low preoperative body mass index [BMI < 20.3 kg/m^2, hazard ratio (HR) 1.646, $P = 0.0190$] and adjuvant chemotherapy (not-completed, HR 1.652, $P = 0.0170$) as independent prognostic factors. In patients with a history of gastrectomy, there were significantly more patients with poor prognostic factors, including a low preoperative BMI ($P = 0.0009$) and low completion rate of adjuvant chemotherapy ($P = 0.0294$) as compared with those without a history of gastrectomy. A low preoperative BMI significantly reduced the completion rate of adjuvant chemotherapy ($P = 0.0186$), which may lead to poor prognostic outcomes. In conclusion, perioperative nutritional management is important to reduce postoperative BMI loss and obtain a better prognosis after a pancreatectomy for PDAC in patients with a history of gastrectomy.

Keywords: a history of gastrectomy; body mass index; pancreatectomy; pancreatic ductal adenocarcinoma
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Introduction

The prevalence of elderly patients with a history of abdominal surgery has been increasing as the average lifespan has increased in Japan. Furthermore, the incidence of pancreatectomy for patients with a history of upper abdominal surgery has also been increasing.

The treatment outcomes of patients with a gastric carcinoma have improved in Japan due to the development of a group medical screening system and progress in diagnostic techniques, adjuvant chemotherapy, and surgical procedures. According to the Editorial Board of the Cancer Statistics in Japan (2021), the number of long-term survivors after gastric carcinoma resection is increasing. According to data obtained from cancer registries of 22 prefectures, the 5-year relative survival rate for gastric carcinoma diagnosed during 2009-2011 was 66.6%.

Pancreatic ductal adenocarcinoma (PDAC) is a disease with a poor prognosis despite curative resection. Upon the introduction of adjuvant chemotherapy after pancreatectomy with gemcitabine (GEM; CONKO-001; Charite Onkologie) (Oettle et al. 2013) or TS-1 (S-1; Taiho Pharmaceutical, Tokyo, Japan; JASPAC 01; the Japan Adjuvant Study Group of Pancreatic Cancer) (Uesaka et al. 2016), the postoperative 5-year overall survival rates (OS) increased to 24.4% and 44.1%, respectively, which were significantly better than the 5-year OS (10.4%) of patients treated with surgery alone. Although the completion of adjuvant chemotherapy predicts survival in patients undergoing pancreatectomy for PDAC, the reported completion rate of adjuvant chemotherapy (62%-76%) is less than satisfactory (Ueno at al. 2009; Oettle et al. 2013; Uesaka et al. 2016). Those patients could not complete adjuvant chemotherapy due to their nutritional status and perioperative

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complications.

In patients with a history of gastrectomy, a pancreatectomy is usually limited by adhesions, and more complicated procedures are often required, such as adhesiotomy, preservation of the remnant stomach and jejunal loop, and reconstruction after pancreatectomy, compared to a pancreatectomy in those without a history of gastrectomy.

Body weight loss (BWL) is a common finding in patients with a history of gastrectomy (Kim et al. 2017). Previous studies have demonstrated that the average BWL was approximately 10%-20% of the preoperative body weight, and severe BWL was a poor prognostic factor (Park et al. 2018). The average (± standard deviation) of the perioperative loss in body mass index (BMI) was also reported at 2.2 ± 1.9 kg/m^2 in patients undergoing gastrectomy. Excessive weight loss and malnutrition, which may lead to a poor outcome, are associated with failure to complete adjuvant chemotherapy (Aoyama et al. 2013). In patients with a history of gastrectomy, a pancreatectomy may result in a poor outcome based on a low nutritional status as well as the complexity of the surgical procedure due to adhesions, as compared with those without a history of gastrectomy.

The aim of this study was to clarify the impact of a history of gastrectomy in patients undergoing a pancreatectomy for PDAC. We investigated the clinical course of 28 patients with a history of gastrectomy compared to that of 279 patients without this history. The factors of the clinical course that were compared include surgical procedures and prognostic outcomes.

Methods

Study population

Between January 2005 and December 2019, 307 pancreatectomies for PDAC were performed, including 192 pancreatoduodenectomies (PDs) and 115 distal pancreatectomies (DPs). Twenty-eight patients (9.1%) had a history of gastrectomy (PD 14, DP 14), while 279 patients did not (PD 178, DP 101). Operative methods of gastrectomy were distal gastrectomy (DG) reconstructed with the Billroth I method (DGBI) in 10 patients, DG reconstructed with the Billroth II method (DGBII) in 5, DG reconstructed with the Roux-en-Y method (DGRY) in 2, proximal gastrectomy (PG) reconstructed with an esophagus-stomach anastomosis in 2, and total gastrectomy (TG) reconstructed with an esophagus-jejunum anastomosis in 9 (Table 1). The diseases for gastrectomy were stomach carcinoma in 21 patients and gastroduodenal ulcer in 7. The intervals from gastrectomy to pancreatectomy were less than 10 years in 13 patients, 10 to 20 years in 5, and more than 20 years in 10.

The clinical stage due to UICC classification of all 307 PDAC patients was as follows: Stage 0, 1 patient(s); IA, 25; IB, 53; IIA, 21; IIB, 123; III, 49; IV, 35. The 307 PDAC patients comprised 28 PDAC patients with a history of gastrectomy (Stage 0, 0 patients; IA, 6; IB, 7; IIA, 1; IIB, 7; III, 2; IV, 5) and 279 patients without history (Stage 0, 1 patient; IA, 19; IB, 46; IIA, 20; IIB, 116; III, 47; IV, 30).

Procedure of pancreatectomy and definition of complications

We usually performed a subtotal stomach-preserving pancreatoduodenectomy (SSPPD), reconstructed according to the modified Child's technique (in order of pancreas, bile duct, and stomach with jejunum). The pancreatojejunostomy was performed according to a modified Kakita anastomosis (Kakita et al. 1996), or Blumgart anastomosis (Grobmyer et al. 2010). In a distal pancreatectomy, pancreas isolation using an auto-suture device is usually performed.

When the patient had serious complications of grade III or more in the Clavien-Dindo classification system, we defined them as postoperative complications (Katayama et al. 2016). As for a postoperative pancreatic fistula (POPF) (Bassi et al. 2005) and delayed gastric emptying (DGE) (Wente et al. 2007), we defined grades B and C as postoperative complications.

Adjuvant chemotherapy

Adjuvant chemotherapy was completed in 191 patients (62.2%) (Table 2): 172 patients had postoperative adjuvant chemotherapy, including 74 patients with GEM alone according to CONKO-001 (Oettle et al. 2013), 97 patients with S-1 alone according to JASPAC 01 (Uesaka et al. 2016), and one with capecitabine plus oxaliplatin (XELOX). The duration of the postoperative adjuvant chemotherapy was 6 months.

Nineteen patients underwent a preoperative neoadjuvant chemotherapy (NAC), including 11 patients with both GEM and S-1 (GS) according to Prep-02/JSAP05 (Unno et al. 2019; Motoi et al. 2019), 6 patients with GEM plus nab-Paclitaxel (GnP), and 2 patients with FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). A preoperative NAC-GS was performed for resectable PDAC after the report of Prep-02/JSAP05 on January 2019 (Unno et al. 2019), and was administered for 2 months, followed by surgery and postoperative S-1 for 6 months. NAC with GnP (Truty et al. 2021) or FOLFIRINOX (Janssen et al. 2019) was performed for borderline resectable PDAC, and was administered for 6 to 8 months, followed by surgery and the same protocol postoperatively for 6 months. In 28 patients with a history of gastrectomy, 12 patients (42.9%) could complete adjuvant chemotherapy, including 4 patients with postoperative GEM, 7 patients with postoperative S-1, and one with NAC-Gnp.

Adjuvant chemotherapy was not completed in 116 patients (37.8%) for the following reasons: 43 had poor performance status, 20 were elderly (80 years old or older), 18 refused chemotherapy, 2 were not able to continue chemotherapy because of the side effects, and 33 had an early diagnosis of carcinoma recurrence before completion of postoperative adjuvant chemotherapy.

Table 1. Characteristics of 28 patients with a history of gastrectomy who underwent pancreatectomy for pancreatic ductal adenocarcinoma (PDAC).

		Re-construction methods after gastrectomy					Stomach disease		After gastrectomy (years)		
	Total	DG			PG	TG	Carcinoma	Ulcer	< 10	10-20	20 <
		BI	BII	RY							
PD	14	5	2	1	1	5	10	4	6	3	5
DP	14	5	3	1	1	4	11	3	7	2	5
Total	28	10	5	2	2	9	21	7	13	5	10

PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DG, distal gastrectomy; PG, proximal gastrectomy; TG, total gastrectomy; BI, Billroth I method; BII, Billroth II method; RY, Roux-en-Y method.

Table 2. Type and completion rate of adjuvant chemotherapy and the reason for non-completion.

	History of gastrectomy			
	Total	Without	With	
Adjuvant chemotherapy	307	279	28	
Completion	191	179	12	*P*-value
(Rate)	62.2%	64.2%	42.9%	0.0294
Postoperative chemotherapy				
GEM	74	70	4	
S-1	97	90	7	
XELOX	1	1	0	
Preoperative NAC				
GS	11	11	0	
GEMnab-PTX	6	5	1	
FOLFIRINOX	2	2	0	
Non-Completion	116	100	16	
(Rate)	37.8%	35.8%	57.1%	
Reason				
Poor performance status	43	36	7	
Early cancer recurrence	33	28	5	
Age > 80 years	20	17	3	
Refused	18	17	1	
Side effect	2	2	0	

GEM, gemcitabine; S-1, TS-1; XELOX, capecitabine plus oxaliplatin; NAC, neoadjuvant chemotherapy; GS, gemcitabine and TS-1; GEMnab-PTX, gemcitabine plus nab-Paclitaxel; FOLFIRINOX, oxaliplatin, irinotecan, fluorouracil, and leucovorin.

Comparison of the clinical course after pancreatectomy for PDAC between the patients with and without a history of gastrectomy

We investigated the clinical course of 307 patients who underwent pancreatectomy for PDAC and clarified the impact of a history of gastrectomy. We compared the difference in clinical course between the patients with and without a history of gastrectomy.

The patients were evaluated for overall perioperative status, including inflammatory and nutritional status using the modified Glasgow prognostic score [mGPS: C-reactive protein (CRP) > 1.0 mg/dL and serum albumin level < 3.5 g/dL, Score 2; CRP > 1.0 mg/dL, Score 1; and CRP ≤ 1.0 mg/dL, Score 0], the prognostic nutritional index (PNI: 10 × serum albumin level in g/dL + 0.005 × peripheral blood lymphocytes in mm^3), the neutrophil/lymphocyte ratio (NLR: neutrophils/lymphocytes in mm^3/mm^3), and the platelet/lymphocyte ratio (PLR: platelets/lymphocytes in $\mu l/mm^3$) (Watanabe et al. 2016). BMI (body weight divided by height squared in kg/m^2) (Park et al. 2018) and perioperative BWL [% BWL: (preoperative body-weight – postoperative body-weight) × 100/preoperative body weight]

(Aoyama et al. 2013) were also used for the assessment. The calculation of these indexes was carried out within 1 week before the surgery and 4-8 weeks after surgery.

A receiver-operating characteristic curve analysis was performed and the Youden Index was calculated to determine cut-off values (Donizy et al. 2014). We established the effective cut-off levels for each value so that the difference in the survival rates between both groups became maximum. We categorized each group based on the preoperative age (< 75 and ≥ 75 years), albumin (> 3.4 and ≤ 3.4 g/dl), total bilirubin (< 1.8 and ≥ 1.8 mg/dl), hemoglobin (> 10.9 and ≤ 10.9 g/dl), BMI (≥ 20.3 and < 20.3 kg/m^2), PNI (≥ 45 and < 45), mGPS score (0, and 1 or 2), PLR (< 183 and ≥ 183), NLR (< 2.7 and ≥ 2.7), perioperative BWL (< 9.4 and ≥ 9.4 %), BMI loss (< 2.3 and ≥ 2.3 kg/m^2), UICC TNM classification (0/IA/IB/IIA and IIB/III/IV), operative time (< 410 and ≥ 410 min), blood loss (< 778 and ≥ 778 ml), and length of hospital stay (< 19 and ≥ 19 days), and we evaluated patient characteristics, the perioperative course, completion rate of adjuvant chemotherapy, and prognostic outcomes. As for CA19-9, we used the cut-off value of our institute (≤ 37 and > 37 U/ml).

In the multivariate analysis to determine the prognostic factors associated with OS, we excluded the patients who could not complete adjuvant chemotherapy because of the early recurrence of PDAC within 6 months postoperatively so that the decrease in completion rate of the adjuvant chemotherapy due to the early recurrence of PDAC did not influence a prognostic evaluation.

Statement of ethics

The present study was reviewed and approved by the Ethics Committee of the Saitama Cancer Center, Japan (Project No.1164). Patients were not required to provide informed consent to the study as the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Follow-up and analysis of the clinical course after pancreatectomy

Clinical data were obtained from the patients' medical records. Most of the patients were regularly screened for carcinoma recurrence with contrast-enhanced computed tomography or ultrasonography (US) every 3-6 months. The postoperative periodical surveillance was customarily conducted for 5 years after surgery. Thereafter, we usually recommend annual cancer screening. Postoperative surveillance after the pancreatectomy included investigation of the presence or absence of malnutrition, fatty liver, and diabetes due to pancreatic insufficiency.

Statistical analysis

Categorical variables were assessed using the Chi-squared test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Wilcoxon rank-sum test or Student t-test. The OS was evaluated using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards analysis was used to perform multivariate analyses to determine the prognostic factors and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). *P*-values of < 0.05 were considered statistical significance. All statistical analyses were performed using the JMP software program (v.11 SAS Institute Inc., Cary, NC, USA).

Results

Comparison of the characteristics of patients with and without a history of gastrectomy

We compared the characteristics of the patients with and without a history of gastrectomy according to patient factors, inflammation and nutritional factors, tumor factors, and treatment factors. The patients were divided into two categories in each variable according to cut-off value as good or poor prognostic group (Table 3). In patients with a history of gastrectomy, there were significantly more patients in the poorer prognostic category for four factors, including sex (male, $P = 0.0002$), low preoperative BMI ($P = 0.0009$), high preoperative CA19-9 ($P = 0.0234$), and high non-completion rate of adjuvant chemotherapy ($P = 0.0294$). On the other hand, in the patients without a history of gastrectomy, there were significantly more patients in the poorer prognostic category for two factors, including a low preoperative PNI ($P = 0.0081$) and positive rate of lymph-node metastasis ($P = 0.0072$).

Comparison of the perioperative course of pancreatectomy for PDAC between the patients with and without a history of gastrectomy

In patients with a history of gastrectomy, the average (± standard error) operative time of the PD and DP, and blood loss of the DP were 503.5 ± 37.4 min, 301.8 ± 34.1 min, and 543.3 ± 129.1 ml, respectively, which showed no significant difference as compared with that of the operative time of SSPPD (470.7 ± 7.2 min, $P = 0.2394$), DP (294.9 ± 9.0 min, $P = 0.8010$), and blood loss of DP (593.4 ± 56.9 ml, $P = 0.7553$) in the patients without a gastrectomy (Table 4). On the other hand, in patients with a history of gastrectomy, the average of blood loss of the PD was 2286.9 ± 902.5 ml, which was significantly more as compared with that of the SSPPD (1183.5 ± 66.8 ml) in patients without a gastrectomy ($P = 0.0015$).

In patients with a history of gastrectomy, the incidence of all postoperative complications after a PD was 50.0%, which showed no significant difference as compared with that after a SSPPD (29.2%) in the patients without a gastrectomy ($P = 0.1179$). The incidence of POPF after PD (28.6%) was significant more as compared with that after a SSPPD (9.6%) in patients without a gastrectomy ($P = 0.0281$). A significant difference was not found between the groups after a DP ($P = 0.4616$).

Table 3. Comparison of the categorical distribution due to the cut-off value of each variable between the patients with and without a history of gastrectomy.

					History of gastrectomy		
					Without	With	
	Cut off value				279	28	
	Good	n	Poor	n	n (%)	n (%)	*P*-value
Patient factors							
Age	< 75 years	224	≥ 75 years	83	71 (25.4)	12 (42.9)	0.0579
Sex	Female	141	Male	166	142 (50.9)	24 (85.7)	0.0002
Preoperative albumin	> 3.4 g/dl	268	≤ 3.4 g/dl	39	38 (13.6)	1 (3.6)	0.0811
Preoperative total bilirubin	< 1.8 mg/dl	265	≥ 1.8 mg/dl	42	41 (14.7)	1 (3.6)	0.0602
Preoperative hemoglobin	> 10.9 g/dl	255	≤ 10.9 g/dl	52	45 (16.1)	7 (25.0)	0.2554
Inflammatory and nutritional factors							
Perioperative BWL	< 9.4 %	190	≥ 9.4 %	117	104 (37.3)	13 (46.4)	0.3467
Preoperative BMI	≥ 20.3 kg/m^2	210	< 20.3 kg/m^2	97	80 (28.7)	17 (60.7)	0.0009
Perioperative BMI Loss	< 2.3 kg/m^2	218	≥ 2.3 kg/m^2	89	82 (29.4)	7 (25.0)	0.6208
Preoperative PNI	≧ 45	212	< 45	95	92 (33.0)	3 (10.7)	0.0081
Preoperative mGPS	0	246	1 or 2	61	58 (20.8)	3 (10.7)	0.1738
Preoperative PLR	< 183	224	≥ 183	83	78 (28.0)	5 (17.9)	0.2330
Preoperative NLR	< 2.7	187	≥ 2.7	120	112 (40.1)	8 (28.6)	0.2228
Tumor factors							
Location	Body-Tail	115	Head	192	178 (63.8)	14 (50.0)	0.1564
Preoperative CA19-9	≤ 37 U/ml	51	> 37 U/ml	255	228 (82.0)	27 (96.4)	0.0234
Portal vein invasion	(−)	203	(+)	104	91 (32.6)	13 (46.4)	0.1494
Nerve plexus invasion	(−)	232	(+)	75	71 (25.5)	4 (14.3)	0.1671
Lymph-node metastasis	(−)	103	(+)	204	192 (68.8)	12 (42.9)	0.0072
Surgical margin	(−)	223	(+)	82	78 (28.2)	4 (14.3)	0.0943
M-factor	(−)	272	(+)	35	30 (10.8)	5 (17.9)	0.2889
UICC TNM classification	0/IA/IB/IIA	100	IIB/III/IV	207	193 (69.2)	14 (50.0)	0.0450
	1/25/53/21		123/49/35				
Adjuvant chemotherapy	Completed	191	Not-completed	116	100 (35.8)	16 (57.1)	0.0294
Except early recurrence		191		83	72 (28.7)	11 (47.8)	0.0651
Due to early recurrence		0		33	28 (10.0)	5 (17.9)	0.2352
Treatment factors							
Operative time	< 410 min	155	≥ 410 min	152	142 (50.9)	10 (35.7)	0.1230
Blood loss	< 778 ml	153	≥ 778 ml	154	139 (49.8)	15 (53.6)	0.7050
Complication	(−)	201	(+)	106	92 (33.0)	14 (50.0.)	0.0774
Length hospital stay	< 19 days	110	≥ 19 days	197	180 (64.5)	17 (60.7)	0.6909
Blood transfusion	(−)	236	(+)	71	62 (22.2)	9 (32.1)	0.2516

BWL, body weight loss; BMI, body mass index; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

The impact of nutritional status and clinicopathological characteristics on the prognosis of patients undergoing a pancreatectomy for PDAC

In all 307 patients of PDAC, after the median observation period of 21.5 months (range 3.0-172.3 months), the 5-year OS and the median survival time after pancreatectomy were 32.0% and 21.5 months, respectively. In the patients with a history of gastrectomy, the 5-year OS and the median survival time after pancreatectomy were 17.6% and 16.8 months, respectively. These results showed a relatively poorer prognosis compared with 33.4% and 22.0 months in the patients without this history (P = 0.1329) (Fig. 1). However, this comparison did not show a significant difference because the number of patients recorded was insufficient.

Univariate and multivariate analyses were conducted to determine the prognostic factors associated with OS after pancreatectomy for PDAC (Table 5). A multivariate analysis revealed that 6 variables were significantly associated with a better prognosis, viz. female [hazard ratio (HR)

Table 4. Comparison of the perioperative course after pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) between the patients with and without a history of gastrectomy.

		History of gastrectomy				
		Without		With		
Pancreaticoduodenectomy (PD)		n = 178		n = 14		
		Average	± S.E.	Average	± S.E.	*P*-value
Operative Time	min	470.7	± 7.2	503.5	± 37.4	0.2394
Blood Loss	ml	1183.5	± 66.8	2286.9	± 902.5	0.0015
	Total	n	(%)	n	(%)	
Complication*	59	52	29.2	7	50.0	0.1179
POPF (Grade B/C)	21	17	9.6	4	28.6	0.0281
DGE (Grade B/C)	23	23	12.9	0	0	0.0538
Other**	15	12	6.7	3	21.4	0.0923
Mortality	0	0		0		N.E.
Distal pancreatectomy (DP)		n = 101		n = 14		
		Average	± S.E.	Average	± S.E.	*P*-value
Operative Time	min	294.9	± 9.0	301.8	± 34.1	0.8010
Blood Loss	ml	593.4	± 56.9	543.3	± 129.1	0.7553
	Total	n	(%)	n	(%)	
Complication*	47	40	39.6	7	50.0	0.4616
POPF (Grade B/C)	35	31	30.7	4	28.6	0.8709
DGE (Grade B/C)	4	2	2.0	2	14.3	0.0579
Other**	8	7	6.9	1	7.1	0.9768
Mortality		0		0		N.E.

*Grade III or more by Clavien-Dindo classification.
**Other complications included pneumonia, biliary fistula, lymphorrhea, intestinal obstruction, abscess, hemorrhage, and excessive ascites.
POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; N.E., not examined; S.E., standard error.

1.778, 95% confidence interval (CI) 1.230-2.594, P = 0.0021], high preoperative BMI (HR 1.646, 95% CI 1.086-2.485, P = 0.0190), high preoperative PNI (HR 1.642, 95% CI 1.049-2.544, P = 0.0302), low preoperative CA19-9 (HR 1.899, 95% CI 1.175-3.227, P = 0.0078), high completion rate of adjuvant chemotherapy (HR 1.652, 95% CI 1.096-2.466, P = 0.0170), and short operative time (HR 1.620, 95% CI 1.025-2.588, P = 0.0389).

Among the factors influencing the completion rate of adjuvant chemotherapy (Table 6), 13 of 25 valuables showed a significant difference, including age (P < 0.0001), preoperative albumin (P = 0.0004), hemoglobin (P = 0.0014), BMI (P = 0.0186), PNI (P < 0.0001), mGPS (P = 0.0038), PLR (P = 0.0009), NLR (P = 0.0104), perioperative blood loss (P = 0.0011), complications (P = 0.0491), length hospital stay (P = 0.0018), blood transfusion (P < 0.0001), and a history of gastrectomy (P = 0.0294). Low preoperative BMI was one of four factors which showed significantly more patients in the poorer prognostic category (< 20.3 kg/m^2) in the patients with a history of gastrectomy, as compared with the patients without a gastrectomy (Table 3).

Comparison of the recurrence pattern after PDAC resection between the patients with and without a history of gastrectomy

In 28 patients with a history of gastrectomy, 21 patients (75.0%) experienced a recurrence after PDAC resection, and 20 of them had distant metastasis (95.2%), which was significantly more recurrence with distant metastasis as compared with that in the patients without (74.1%, P = 0.0130) (Table 7). As for local recurrence, there was no significant difference between the groups (19.0% vs. 35.3%, P = 0.1169). The ratio of the distant metastasis did not show a significant difference between the patients with or without completion of adjuvant chemotherapy (72.1% vs. 81.7%, P = 0.0934). However, the patients without completion of adjuvant chemotherapy experienced significantly more recurrences with liver metastases as compared with the patients who completed adjuvant chemotherapy (46.2% vs. 20.9%, P < 0.0001).

Regarding chemotherapy after the postoperative recurrence of PDAC in patients with a history of gastrectomy, there were significantly more patients who could not undergo chemotherapy, as compared with that in patients

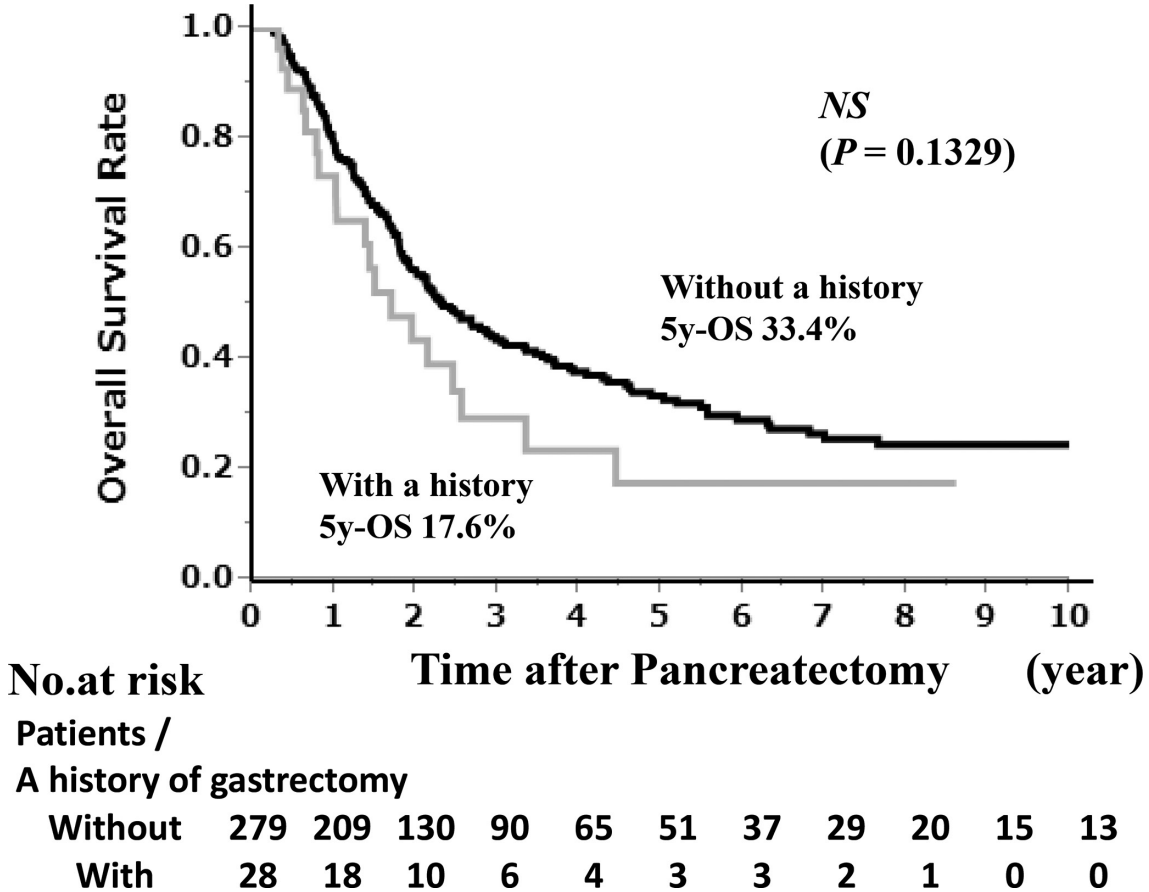

Fig. 1. The difference in overall survival rate after pancreatectomy for PDAC between the patients with and without a history of stomach resection.
In 28 patients with a history of gastrectomy, the 5-year OS after pancreatectomy for PDAC was 17.6% (Grey line), which showed a relatively poorer prognosis compared with the rate of 33.4% in 279 patients without this history (Black line). However, this comparison did not show a significant difference because the number of patients recorded was insufficient ($P = 0.1329$).

without this history (66.7% vs. 37.8%, $P = 0.0111$). Those who could not undergo chemotherapy underwent a palliative care therapy instead.

Discussion

The number of surgeries for elderly patients has increased in recent years in line with increases in the elderly population. On October 1, 2019, the total population of Japan was 126,170,000 people, 35,890,000 or 28.4% of which were 65 years or older (Cabinet Office Japan 2020). In 1970, this value was only at 7.1% (7,400,000).

In this study, 28 patients (9.1%) among 307 who underwent pancreatectomy for PDAC had a history of gastrectomy. In our previous study (Amikura et al. 2020), among 4,883 patients who were surgically treated for gastric carcinoma, 529 patients (10.8%) had postoperative metachronous multiple primary cancers. Thirty-seven patients had PDAC (7.0%) and 34 patients died of cancer within an observation period (91.9% of the cancer mortality rate).

As for the operative procedure of pancreatectomy in patients with a history of gastrectomy, a more complicated surgical procedure was usually required than in those without a gastrectomy. Adhesiotomy and preservation of the remnant stomach or the jejunum loop are important components of the procedure. Adhesions may develop due to postoperative pancreatitis or a pancreatic fistula in addition to gastrectomy and lymph-node dissection (Guerra et al. 2017). In the patients with a history of gastrectomy, the average of blood loss and the incidence of POPF of PD were significantly more compared with that of SSPPD in those without a gastrectomy. However, there was no significant difference in operative time, blood loss, and incidence of complications after DP between the groups (Table 4).

The patients with a history of gastrectomy may have postgastrectomy anemia, which is caused by deficiencies in iron, vitamin B12, and folic acid (Kim et al. 2018). However, in this study, there was no significant difference between the patients with and without a history of gastrectomy in the average preoperative hemoglobin level (average ± S.E.; 12.1 ± 0.3 vs. 12.3 ± 0.1, $P = 0.4101$) and the number of patients who showed a low preoperative hemoglobin

Table 5. Univariate and multivariate analyses were conducted to determine the prognostic factors associated with 5-year overall survival (OS) in the patients who underwent pancreatectomy for pancreatic ductal adenocarcinoma (PDAC).

		5-year OS			5-year OS		Univariate	Multivariate		
Total n = 307	Good	n	(%)	Poor	n	(%)	*P*-value	*P*-value	HR	(95%CI)
Patient factors										
Age	< 75 years	224	33.9	≥ 75 years	83	27.6	0.0435	0.4440	1.201	(0.746-1.893)
Sex	Female	141	40.7	Male	166	24.5	0.0051	0.0021	1.778	(1.230-2.594)
Preoperative albumin	> 3.4 g/dl	268	35.5	≤ 3.4 g/dl	39	8.4	< 0.0001	0.2865	1.554	(0.695-3.612)
Preoperative total bilirubin	< 1.8 mg/dl	265	35.0	≥ 1.8 mg/dl	42	13.7	0.0011	0.9166	1.027	(0.632-1.721)
Preoperative hemoglobin	> 10.9 g/dl	255	34.5	≤ 10.9 g/dl	52	20.3	0.0010	0.7477	1.091	(0.647-1.880)
Inflammatory and nutritional factors										
Perioperative BWL	< 9.4 %	190	38.7	≥ 9.4 %	117	20.2	0.0059	0.7380	1.104	(0.630-2.018)
Preoperative BMI	≥ 20.3 kg/m^2	210	42.0	< 20.3 kg/m^2	97	12.1	< 0.0001	0.0190	1.646	(1.086-2.485)
Perioperative BMI Loss	< 2.3 kg/m^2	218	36.2	≥ 2.3 kg/m^2	89	21.1	0.0115	0.1868	1.538	(0.815-2.989)
Preoperative PNI	≥ 45	212	44.2	< 45	95	6.2	< 0.0001	0.0302	1.642	(1.049-2.544)
Preoperative mGPS	0	246	37.8	1 or 2	61	7.2	< 0.0001	0.4017	1.324	(0.671-2.428)
Preoperative PLR	< 183	224	36.2	≥ 183	83	18.7	0.0016	0.5758	1.135	(0.732-1.786)
Preoperative NLR	< 2.7	187	38.8	≥ 2.7	120	21.3	0.0090	0.4521	1.164	(0.781-1.720)
Tumor factors										
Location	Body-Tail	115	42.4	Head	192	25.6	0.0010	0.9835	1.005	(0.623-1.631)
Preoperative CA19-9	≤ 37 U/ml	51	58.6	> 37 U/ml	255	25.5	0.0001	0.0078	1.899	(1.175-3.227)
Portal vein invasion	(−)	203	36.2	(+)	104	23.5	0.0668			
Nerve plexus invasion	(−)	232	36.7	(+)	75	18.2	0.0060	0.9024	1.026	(0.672-1.546)
Lymph-node metastasis	(−)	103	49.1	(+)	204	23.5	0.0004	0.1861	6.086	(0.303--39.999)
Surgical margin	(−)	223	38.6	(+)	82	17.0	0.0006	0.0528	1.518	(0.995-2.293)
M-factor	(−)	272	35.2	(+)	35	8.7	< 0.0001	0.4757	1.364	(0.675-2.519)
UICC TNM classification	0/IA/IB/IIA	100	50.0	IIB/III/IV	207	23.4	0.0001	0.1840	6.246	(0.305-42.898)
Adjuvant chemotherapy	Completed	191	40.9	Not-completed	116	15.8	< 0.0001			
Except early recurrence		191	39.0		83	21.3	< 0.0001	0.0170	1.652	(1.096-2.466)
Treatment factors										
Operative time	< 410 min	155	42.2	≥ 410 min	152	21.5	0.0001	0.0389	1.620	(1.025-2.588)
Blood loss	< 778 ml	153	46.3	≥ 778 ml	154	18.4	< 0.0001	0.2940	1.252	(0.823-1.909)
Complication	(−)	201	32.0	(+)	106	31.7	0.8976			
Length hospital stay	< 19 days	110	44.2	≥ 19 days	197	25.2	< 0.0001	0.0516	1.449	(0.997-2.135)
Blood transfusion	(−)	236	33.7	(+)	71	26.1	0.0011	0.3029	1.292	(0.797-2.140)
History of gastrectomy	(−)	279	33.4	(+)	28	17.6	0.1329			

BWL, body weight loss; BMI, body mass index; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

(< 10.9 g/dl) (7 patients and 25.0% vs. 45 patients and 16.1%, $P = 0.2554$). Patients with PDAC may present with preoperative anemia caused by metabolic disorders, or a duodenal hemorrhage due to the PDAC invasion.

Regarding patients who underwent DGBI, we must be careful about the adhesiotomy around the BI anastomotic region from a lateral segment of the liver, pancreas, and the common hepatic artery. In the patients who underwent DGBII, DGRY, or TG, it is necessary to exfoliate the adhesion so as not to injure the blood supply of the remnant stomach or the jejunal loop during DP. During PD, we have to utilize a more distal jejunum loop, because gastro-jejunostomy or esophago-jejunostomy using the jejunum loop was already done in these patients, which complicates the reconstruction after pancreatectomy. Furthermore, there may be massive adhesion particularly in those with a history of bowel obstruction after a gastrectomy. A patient with a history of DGBI died of postoperative hemorrhage after PD due to a mixed type of intraductal papillary mucinous neoplasm (IPMN). He had a three-time history of bowel obstruction surgery after DGBI. Jejunal perforation and hemorrhage might occur postoperatively at the site where the intestinal injury was repaired during the adhesiotomy. The definitive histological diagnosis was IPMN with carcinoma *in situ*. We must pay attention not to injure the jejunal loop during adhesiotomy, particularly in patients with a history of bowel obstruction surgery.

The stomach usually has five feeding arteries, including the right and left gastric artery (RGA and LGA), right and left gastroepiploic artery (RGEA and LGEA), and short gastric artery (SGA). During DG for gastric carcinoma, the RGA, LGA, and RGEA are usually cut and divided, leaving the LGEA and SGA as the remaining blood supply of the remnant stomach after the DG. The LGA may remain after DG for a gastroduodenal ulcer. For those with a history of DG, remnant stomach ischemia is a concern, since the blood flow from the LGEA and SGA may have been ligated during DP. However, we did not experience any cases in which ischemia of the remnant stomach after DP occurred. Two patients required the total resection of the remnant

Table 6. Factors influencing the completion rate of adjuvant chemotherapy in the preoperative nutritional evaluation.

	Completion rate of adjuvant chemotherapy								
	Good	Total	Complete	(%)	Poor	Total	Complete	(%)	*P*-value
Patient factors									
Age	< 75 years	224	158	70.5	≥ 75 years	83	33	39.8	< 0.0001
Sex	Female	141	91	64.5	Male	166	100	60.2	0.4385
Preoperative albumin	> 3.4 g/dl	268	177	66.0	≤ 3.4 g/dl	39	14	35.9	0.0004
Preoperative total bilirubin	< 1.8 mg/dl	265	169	63.8	≥ 1.8 mg/dl	42	22	52.4	0.1617
Preoperative hemoglobin	> 10.9 g/dl	255	169	66.3	≤ 10.9 g/dl	52	22	42.3	0.0014
Inflammatory and nutritional factors									
Perioperative BWL	< 9.4 %	190	124	65.3	≥ 9.4 %	117	67	57.3	0.1614
Preoperative BMI	≥ 20.3 kg/m^2	210	140	66.7	< 20.3 kg/m^2	97	51	52.6	0.0186
Perioperative BMI Loss	< 2.3 kg/m^2	218	142	65.1	≥ 2.3 kg/m^2	89	49	55.1	0.1003
Preoperative PNI	≥ 45	212	149	70.3	< 45	95	42	44.2	< 0.0001
Preoperative mGPS	0	246	163	66.3	1 or 2	61	28	45.9	0.0038
Preoperative PLR	< 183	224	152	67.9	≥ 183	83	39	47.0	0.0009
Preoperative NLR	< 2.7	187	127	67.9	≥ 2.7	120	64	53.3	0.0104
Tumor factors									
Location	Body-Tail	115	78	67.8	Head	192	113	58.9	0.1148
Preoperative CA19-9	≤ 37 U/ml	51	36	70.6	> 37 U/ml	255	155	60.8	0.1808
Portal vein invasion	(−)	203	125	61.6	(+)	104	66	63.5	0.7469
Nerve plexus invasion	(−)	232	141	60.8	(+)	75	50	66.7	0.3575
Lymph-node metastasis	(−)	103	68	63.1	(+)	204	123	61.8	0.3268
Surgical margin	(−)	223	139	62.3	(+)	82	51	62.2	0.9826
M-factor	(−)	272	173	63.6	(+)	35	18	51.4	0.1672
UICC TNM classification	0/IA/IB/IIA	100	67	67.0	IIB/III/IV	207	124	59.9	0.2271
Treatment factors									
Operative time	< 410 min	155	94	60.7	≥ 410 min	152	97	63.8	0.5667
Blood loss	< 778 ml	153	109	71.2	≥ 778 ml	154	82	53.3	0.0011
Complication	(−)	201	133	66.2	(+)	106	58	54.7	0.0491
Length hospital stay	< 19 days	110	81	73.6	≥ 19 days	197	110	55.8	0.0018
Blood transfusion	(−)	236	161	68.2	(+)	71	30	42.3	< 0.0001
History of gastrectomy	Without	279	179	64.2	With	28	12	42.9	0.0294

BWL, body weight loss; BMI, body mass index; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

stomach, including one patient who underwent DP with PDAC invasion to the remnant stomach of DGBII, and another patient who underwent PD with the total resection of the remnant stomach of PG prophylactically.

In this study, patients with a history of gastrectomy undergoing PDAC resection may have a relatively poorer prognosis compared to those without. To test this hypothesis, we investigated the clinical course after pancreatectomy for PDAC to clarify the difference between the patients with and without a history of gastrectomy. The multivariable analysis of the covariates associated with OS revealed that six variables were significantly associated with a poor prognosis after the PDAC resection, namely being male, low preoperative BMI, low preoperative PNI, high preoperative CA19-9, non-completion of adjuvant chemotherapy, and long operative time (Table 5).

We compared the number of patients between both groups regarding these poor prognostic factors (Table 3). There were significantly more patients with a history of gastrectomy with four of the six factors that the multivariable analysis had revealed as poor prognostic factors, namely being male, low preoperative BMI, high preoperative CA 19-9, and non-completion of adjuvant chemotherapy, as compared with those without it.

The prognostic indicators after pancreatectomy for PDAC; i.e., inflammatory and nutritional factors, including mGPS, PNI, NLR, and PLR, were investigated in several conventional studies. Watanabe et al. (2016) conducted a multivariable analysis that reported PLR as an independent prognostic factor. Similarly, NLR and PNI were reported as independent prognostic factors by Geng et al. (2015) and Asaoka et al. (2016), respectively. However, since these studies analyzed an insufficient number of patients, a future study with more patients is required.

Table 7. Comparison of the recurrence pattern after pancreatic ductal adenocarcinoma (PDAC) resection between the patients with and without a history of gastrectomy.

		History of gastrectomy		
	Total	Without	With	*P*-value
	307	279	28	
Recurrence	222 (72.3%)	201 (72.0%)	21 (75.0%)	0.7365
Distant metastasis	169 (76.1%)	149 (74.1%)	20 (95.2%)	0.0130
Liver	70	65	5	
Lung	24	19	5	
Peritoneal dissemination	37	32	5	
Lymph-node	36	32	4	
Other	2	1 (Bone)	1 (Adrenal grand)	
Local Recurrence	75 (33.8%)	71 (35.3%)	4 (19.0%)	0.1169
Impossible of chemotherapy after recurrence	90 (40.5%)	76 (37.8%)	14 (66.7%)	0.0111

Postoperative adjuvant chemotherapy plays an important role in prognostic improvement after PDAC resection. Patients who underwent postoperative adjuvant chemotherapy had a significantly better prognosis than those treated with surgery alone (Oettle et al. 2013; Uesaka et al. 2016). Studies by Akahori et al. (2016) and Yamada et al. (2017) reported that a low preoperative PNI was significantly associated with failure to complete adjuvant chemotherapy after a PDAC resection.

A low preoperative BMI was found to be a predictor for a poor prognosis after a gastric carcinoma resection (Park et al. 2018). Excessive perioperative BWL was a significant risk factor that induced non-continuity of postoperative adjuvant chemotherapy with S-1, which was one of the reasons why the patients had a poor prognosis after gastric carcinoma resection (Aoyama et al. 2013). Many of the patients who underwent gastrectomy experienced BWL because of decreased food intake after surgery, and did not recover their body weight for a long time (Kim et al. 2017; Park et al. 2018). Since % BWL varies according to height, BMI seems to reflect nutritional status more accurately. In this study, there were significantly more patients with a history of gastrectomy with a low preoperative BMI than those without. As for other inflammatory and nutritional factors, there were no significant differences found between the groups for mGPS, PLR, and NLR. PNI exhibited an inverse relationship. In other words, no significant difference in the overall nutritional status, including an evaluation using data calculated by peripheral blood samples, was found between the groups. Only the patients with a low BMI showed a significant difference regarding the preoperative nutritional status. The non-completion of postoperative adjuvant chemotherapy based on a low preoperative BMI seemed to be one of the important factors for a poor prognosis in patients with a history of gastrectomy after PDAC resection. In the patients with a history of gastrectomy, the 5-year OS in 11 patients with a high preoperative BMI ($\geq$ 20.3 kg/m^2) was 37.4%, which was relatively better than the 7.4% in 17 patients with a low preoperative BMI (< 20.3 kg/m^2), but a significant difference was not found (P = 0.1313).

PDAC patients often cannot undergo postoperative adjuvant chemotherapy. The reported completion rate of adjuvant chemotherapy was 62-76% (Ueno et al. 2009; Oettle et al. 2013; Akahori et al. 2016; Yamada et al. 2017). In this study, 16 of the 28 patients (57.1%) with a history of gastrectomy could not undergo postoperative adjuvant chemotherapy, which were significantly more compared to the patients without this history. Unno et al. (2019) and Motoi et al. (2019) reported that preoperative NAC-GS followed by surgery and postoperative adjuvant S1 could achieve significant survival benefit as compared with upfront surgery followed by adjuvant S1 for PDAC. Preoperative chemotherapy seemed to be provided particularly in the patients with a history of gastrectomy, while their performance status was sufficiently stable. However, approximately half of them were not candidates for preoperative chemotherapy, because preoperative histological diagnosis with endoscopic ultrasonography (EUS) was difficult due to the reconstruction method of gastrectomy. Twelve patients (42.9%), including 4 pancreatic body (TG 4) and 8 pancreatic head (TG 5, DGBII 2 and DGRY 1), were not eligible for a histological diagnosis with EUS and preoperative chemotherapy in this study.

We have three kinds of methods to keep the PDAC patients in good nutritional status during the perioperative

period: managing the nutritional status for a long term after gastrectomy, trying a nutrition care preoperatively, and preventing the perioperative massive bleeding and complications that may deteriorate postoperative nutritional status. First, long-term nutrition education including a control of postgastrectomy anemia and instruction for smoking cessation is necessary after gastrectomy. Second, preoperative management with immune-nutrition should be considered to reduce postoperative weight loss and complications (Ryan et al. 2009; Aida et al. 2014). In the case of upfront surgery without preoperative chemotherapy, we cannot have enough time for preoperative nutritional control of the patients. On the other hand, in the patients with the preoperative chemotherapy, we can improve nutritional status during the chemotherapy. Third, in the perioperative treatment factors, the perioperative massive bleeding (≥ 778 ml), complications onset, long hospital stays (≥ 19 days), and blood transfusion resulted in significantly more BMI loss (≥ 2.3 kg/m^2) after pancreatectomy (P = 0.0018, P = 0.0072, P = 0.0014, and P = 0.0472, respectively). Careful surgery with fewer complications and less blood loss prevents exacerbation of the nutritional status including the postoperative BMI loss and may result in the improvement of the postoperative prognosis.

In patients with a history of gastrectomy, the surgical procedure of pancreatectomy is usually limited due to adhesions. Since the patients usually have a limited range for a perioperative search of the tumor and lymph-node dissection, it was expected that they might have more local recurrences. However, after the PDAC resection in patients with a history of gastrectomy, they had significantly more recurrences with distant metastasis, as compared with those without. It was supposed that the difference in the pattern of carcinoma recurrence was not caused by limitation of the surgical procedure, but by other factors, including the low level of nutrition and immunity, such as low BMI, and also by low completion rate of the adjuvant chemotherapy. Patients without adjuvant chemotherapy had significantly more recurrences with liver metastases, as compared with those treated with adjuvant chemotherapy. Regarding chemotherapy after postoperative recurrence of PDAC, a history of gastrectomy is one of the factors that contribute to a poor postoperative survival rate, since there were significantly more patients who could not undergo chemotherapy after the carcinoma recurrence, as compared with those without a gastrectomy.

A limitation of this study includes the relatively small number of patients from a single-center and its retrospective nature. We attempted to overcome this limitation by employing a long study period, which was necessary to investigate a greater number of patients with a history of gastrectomy undergoing pancreatectomy. Because PD (SSPPD) usually has more surgical invasiveness than DP, we should classify the PDAC patients to PD and DP when we analyze the data of PDAC. In this study, we did not have sufficient number of the PDAC patients and analyzing each operative method separately was difficult. Therefore, we used the total number of PADC patients including both surgery methods for analyses. Future, large-scale multicenter studies are warranted to validate our results.

In conclusion, the complicated surgical procedures, including adhesiotomy in pancreatectomies of patients with a history of gastrectomy, are often required not to injure the blood supply of jejunum loop, the remnant stomach, and the distal jejunum to be used for reconstruction. These patients are not always eligible for postoperative adjuvant chemotherapy and may have a poorer prognosis after the pancreatectomy due to poor nutritional status including low BMI, compared with patients without a history of gastrectomy. Long-term nutrition education is necessary for patients after gastrectomy not to have a poor nutritional status, such as an excessive decrease in BMI. Perioperative nutritional management is important to reduce postoperative BMI loss and complications, and to obtain a better prognosis after pancreatectomy for PDAC.

Author Contributions

K. Amikura participated in manuscript writing, study concept and design, acquisition of data, analysis and interpretation of data, the sequence alignment, drafted the manuscript and revising it critically for important intellectual content. T. Ogura, and A. Takahashi participated in the acquisition, analysis, or interpretation of clinical data and critical revision. All authors helped to perform the research, read and approved the final version of manuscript to be published. And also, all authors had agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors declare no conflict of interest.

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