의학박사 학위논문

Effects of Pancreatectomy on Nutritional State, Pancreatic Function, and Quality of Life over Five Years of Follow Up

췌장절제술이 5년 동안 환자의 영양상태,
췌장 기능 및 삶의 질에 미치는 영향

2021년 2월

서울대학교 대학원

의학과 외과학

신용찬

췌장절제술이 5년 동안 환자의 영양상태, 췌장 기능 및 삶의 질에 미치는 영향

지도교수 장 진 영

이 논문을 의학박사 학위논문으로 제출함

2020 년 10 월

서울대학교 대학원
의학과 외과학 전공
신 용 찬

신용찬의 박사 학위논문을 인준함

2020 년 12 월

위 원 장   류 지 은   (인)

부 위 원 장   장 진 영   (인)

위   원   이 남 준   (인)

위   원   문 정 수   (인)

위   원   박 준 성   (인)

Abstract

Effects of Pancreatectomy on Nutritional State, Pancreatic Function, and Quality of Life over Five Years of Follow Up

Yong Chan Shin

Department of Medicine

The Graduate School

Seoul National University

Background: Despite an increase in long-term survivors after pancreatectomy, few have reported serial changes in symptoms, pancreatic function and QoL based on prospectively developed data sets, with consecutive patients and a predefined follow-up program. This study aimed to analyze serial changes in nutritional status, pancreatic function, and quality of life (QoL) over 5 years of follow-up after pancreatectomy.

Methods: Consecutive patients undergoing pancreaticoduodenectomy (PD) or distal pancreatectomy (DP) between 2007 and 2013 were included in the study. Data on relative body weight (RBW); triceps skinfold thickness (TSFT); body mass index (BMI); serum protein, albumin, transferrin, fasting blood glucose, postprandial 2-h glucose (PP2), glycosylated hemoglobin A1c, insulin, C-peptide, and stool elastase levels; and the European Organization for Research and Treatment of Cancer QLQ-C30/QLQ-PAN26 questionnaire scores were collected serially for 5 years.

Results: Initially, a total of 217 patients were enrolled, but only 79 patients completed the 5-year follow-up. RBW, BMI, and TSFT continued to decrease postoperatively but increased after 6 months. Transferrin, albumin, and protein levels recovered to the preoperative level after 3 months.

Multivariate analysis revealed that a BMI >25 kg/m^2, DP, and adjuvant therapy had a significant impact on endocrine pancreatic insufficiency. Although steatorrhea and diarrhea were mainly resolved by 12 months, the stool elastase level decreased after PD and was not restored. The mean scores for all QoL questionnaires improved above the preoperative value at 12 months postoperatively, except for the diarrhea scale score, which did not recover throughout the study.

Conclusions: Patients undergoing pancreatectomy can return to their daily lives at 12 months postoperatively. However, those with risk factors associated with pancreatic function and QoL need more careful follow-up and supportive management.

……………………………………………………………………………

Contents

List of Tables

List of Figures

Introduction

The number of patients undergoing pancreatectomy is increasing because of increased incidence of benign or malignant periampullary diseases and longer life expectancy[1-6]. However, it may cause impaired pancreatic function[7-9] and ultimately poor quality of life (QoL) in patients. In the last decades, because of the standardization of surgery, multidisciplinary approach, and centralization in high-volume centers[10], the mortality rates have been lower and morbidity rates have been acceptable. This improvement in short-term outcomes led to an increase in long-term survivors after pancreatectomy. Therefore, in the long term, the maintenance of pancreatic function and improvement in QoL have become greatly important for long-term survivors. Previous prospective studies have found a near-normal QoL in patients who underwent middle segmental pancreatic resection[11] and an acceptable QoL in patients who underwent total pancreatectomy compared to that in patients who underwent pylorus-preserving Whipple operation[12]. Fong et al. reported better QoL and physical- and role-functioning scores at 5 years compared to those in age- and sex-matched controls[13]. In a study on long-term QoL and gastrointestinal (GI) functional outcomes after pancreaticoduodenectomy (PD), the authors reported that long-term QoL following PD improves over time; however, it never approaches that of a general healthy population, and GI dysfunction persists in long-term survivors[14]. Moreover, these have had limitations, such as the small number of patients, retrospective study design, lack of a predefined follow-up protocol, and absence of analysis based on serial changes in patients after pancreatectomy. This study was conducted with a prospective design to analyze serial changes in nutritional status, pancreatic function, and QoL on the basis of consecutive and regular follow-up data at 5 years after pancreatectomy.

Material and methods

Patient enrollment and study design

The study included consecutive patients who underwent pancreatectomy (PD and distal pancreatectomy [DP]) for benign or malignant diseases at Seoul National University Hospital between 2007 and 2013 and provided informed consent with long-term follow-up of 5 years. Other pancreatic operations, such as enucleation, central pancreatectomy, and total pancreatectomy, were excluded. After enrollment, some patients were excluded because of (1) resections considered palliative on the basis of unresected disease or distant metastasis, (2) metastasis or recurrence during follow-up, (3) comorbidities more severe than American Society of Anesthesiologists grade III, and (4) previous abdominal operations that might have affected QoL and nutritional status (gastrectomy and colectomy). Some patients were withdrawn from the study because of self-termination of follow-up, local or systemic recurrence, other abdominal operations, and death. Data were collected preoperatively, before discharge and at 3, 6, 12, 24, 36, 48, and 60 months postoperatively. All questionnaires and methods for data collection, storage, and analysis in this study were approved by the Institutional Review Board of Seoul National University Hospital (approval number: H-0801-030-232).

Nutritional assessment

Nutritional status was estimated by relative body weight (RBW) (measured body weight/ideal body weight × 100), triceps skinfold thickness (TSFT), and body mass index (BMI) (measured bodyweight (kg)/measured height (m) squared), and serum protein, albumin, and transferrin levels. The Devine formula was used for the measurement of ideal body weight (Men: 50.0 + 2.3 per each inch over 5 feet (kg), Women: 45.5 + 2.3 per each inch over 5 feet)[15,16]. TSFT were measured on the non-dominant arm according to Frisancho[17].

Pancreatic function

Fasting blood glucose, postprandial 2-h glucose (PP2), and hemoglobin A1c levels were used to assess endocrine pancreatic function. Diagnoses of diabetes mellitus (DM) and impaired fasting glycemia (IFG) were made according to the definitions of the World Health Organization[18] and American Diabetes Association[19]. Patients with preoperative DM were excluded from the endocrine function analysis. Questionnaires about steatorrhea and diarrhea were administered to assess exocrine pancreatic function. Steatorrhea was considered positive for any response worse than a moderate symptom complaint. For diarrhea, the mean symptom score was calculated using the diarrhea item of the symptom scale in the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30[20]. The stool pancreatic elastase level, measured by enzyme-linked immunosorbent assay (BIOSERV Diagnostics, Rostock, Germany), was used as an objective measure of exocrine pancreatic function. Changes in DM or IFG (endocrine), stool elastase level (exocrine), and scores in the questionnaires were used to examine interactions with age, sex, BMI, histology, operation type, history of alcohol use, adjuvant therapy, and complications.

Patients with impaired pancreatic function were treated with pancreatic enzyme supplements or insulin as deemed appropriate clinically.

QoL

QoL was measured using the EORTC QLQ-C30 and QLQ-PAN26 questionnaires[20]. Questionnaires were self-reported by patients, but a trained nurse assisted patients who were unable to do this. Raw data underwent linear transformation to standardize the raw scores, ranging from 0 to 100, as recommended in the EORTC QLQ-C30 and QLQ-PAN26 scoring manual. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale represents a high level of symptomatology. In-hospital complications were graded using the Clavien–Dindo classification[21].

Statistical analysis

Continuous variables are presented as means (standard deviations). Nominal data were compared using χ2 tests or Fisher's exact tests, and continuous variables were compared using Student's t-test or Mann–Whitney U test. Changes over time between groups were evaluated using repeated-measures ANOVA. Paired t-tests were performed to evaluate changes in QoL of patients before and after pancreatectomy.

Factors with P-value <0.100 in the univariable analysis were included in the multivariable analysis. Linear regression analysis was used for continuous variables, and logistic regression analysis was used for categorical (binary) data. Statistical analysis was conducted using SPSS version 21.0 (IBM, Armonk, New York, USA) with P-values <0.05 considered statistically significant.

Results

Patient enrollment and demographic findings

Between October 2007 and February 2013, a total of 217 patients scheduled for pancreatectomy who provided informed consent were enrolled. All of them participated in the study for >1 year postoperatively, but some patients were excluded from the study during the serial follow-up due to outpatient rejection, recurrence of disease, other abdominal operations, and death. Only patients who were followed at the scheduled outpatient visit and answered questionnaires were analyzed for changes in nutritional index, pancreatic function, and QoL after pancreatectomy. The number of patients enrolled in the study during each follow-up period is shown in Table 1.

A total of 148 patients (68.2%) underwent PD and 69 (31.8%) underwent DP. The mean age was 58.8 (11.4) years, and there was a male predominance (1.0:0.8). The mean body weight immediately before surgery was 62.8 (10.4) kg with a mean BMI of 23.8 (3.1) kg/m2. Malignancy was present in 118 patients (54.4%; 51, ampulla of Vater; 24, common bile duct; 31, pancreatic duct; 3, duodenum; 5, intraductal papillary mucinous carcinoma; 1, mucinous cystic carcinoma; 2, metastatic renal cell carcinoma; and 1, leiomyosarcoma). Among 99 patients (45.6%) with benign diseases, 39 had intraductal papillary mucinous neoplasms, 28 had neuroendocrine tumors, 6 had solid pseudopapillary neoplasms, 7 had serous cystic neoplasms, 6 had mucinous cystic neoplasms, 4 had adenomas of the ampulla of Vater, 4 had duodenal GI stromal tumors, 1 had fibrosis of the common bile duct, 2 had benign cyst, 1 had squamous metaplasia, and 1 had calcified degenerative nodule.

The overall morbidity rate was 48.8% (106 of 217). Ten patients had grade I complications (4.6%), 66 had grade II (30.4%), 26 had grade IIIa (12.0%), and 1 had grade IV (0.5%). The single grade IV complication was pseudoaneurysm bleeding.

Table 1. Demographic and clinical characteristics of the patients

	Before surgery (n=217)	3 months (n=185)	6 months (n=188)	12 months (n=194)	24 months (n=174)	36 months (n=144)	48 months (n=116)	60 months (n=79)
Age, mean (SD), year	58.8 (11.4)	58.2 (11.1)	59.2 (10.6)	60.0 (11.2)	60.3 (11.7)	62.1 (11.5)	62.1 (12.6)	64.5 (12.8)
Sex (male:female)	118:99	94:91	101:87	103:91	91:83	80:64	56:60	39:40
Histology, n (%)								
Benign	99 (45.6)	86 (46.5)	87 (46.3)	86 (44.3)	81 (46.6)	67 (46.5)	54 (46.6)	30 (38.0)
Malignant	118 (54.4)	99 (53.5)	101 (53.7)	108 (55.7)	93 (53.4)	77 (53.5)	62 (53.4)	49 (62.0)
Operation type, n (%)								
PD	148 (68.2)	128 (69.2)	129 (68.6)	133 (68.6)	115 (66.1)	102 (70.8)	85 (73.3)	63 (79.7)
DP	69 (31.8)	57 (30.8)	59 (31.4)	61 (31.4)	59 (33.9)	42 (29.2)	31 (26.7)	16 (20.3)
Histologic diagnosis								
AoV cancer	51	46	45	46	43	37	36	25
CBD cancer	24	18	19	20	17	17	12	11
PDAC	31	25	27	29	23	15	10	8
Duodenal cancer	3	2	2	3	2	3	1	1
IPMN	44	34	38	38	36	29	19	18
Endocrine tumor	28	25	23	24	23	19	18	9
SPN	6	6	6	6	6	5	5	2
SCN	7	2	3	4	3	1	1	1
MCN	7	9	8	9	8	6	2	0
Others	16	18	17	15	13	12	12	4

PD, pancreaticoduodenectomy; DP, distal pancreatectomy; AoV, ampulla of Vater; CBD, common bile duct; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm; SPN, solid pseudopapillary neoplasm; SCN, serous cystic neoplasm; MCN, mucinous cystic neoplasm

Nutritional assessment

Changes in nutritional status over the 60 months of follow-up are shown in Figure 1. RBW, BMI, and TSFT continued to decrease postoperatively but began to increase after 6 months, and after 12 months, they recovered to >95% of preoperative levels. Transferrin, albumin, and protein levels were lowest at discharge and had recovered to the preoperative level after 3 months. Repeated-measures ANOVA revealed that the changes in each parameter between the follow-up periods were statistically significant (P<0.001).

Figure 1. Changes in nutritional status: physical parameters (A) and biochemical parameters (B).

RBW, relative body weight; TSFT, triceps skinfold thickness; BMI, body mass index
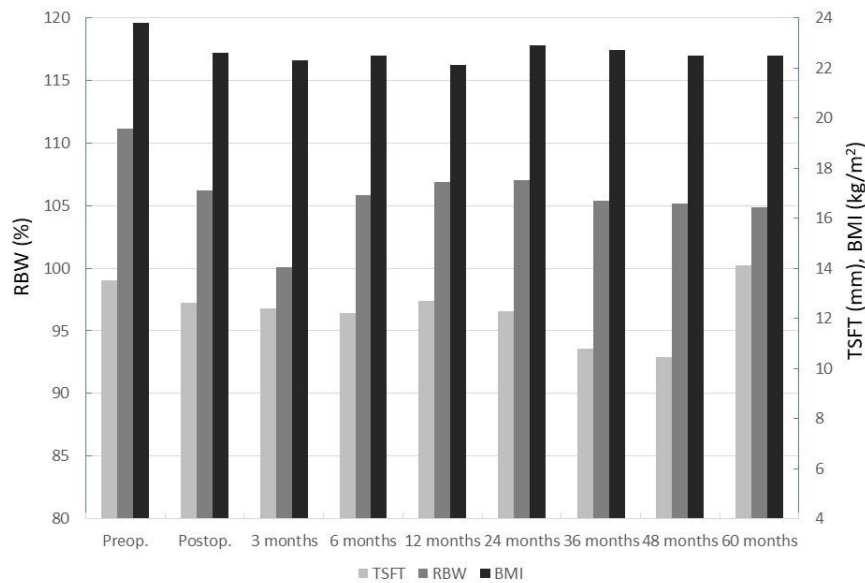
A
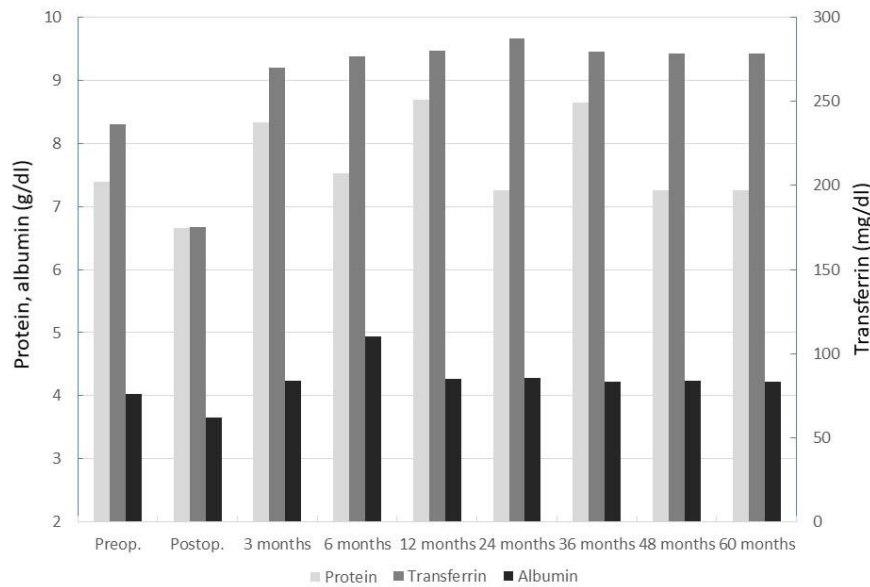
B

Endocrine function

Endocrine pancreatic function was measured serially in 157 patients after the exclusion of 60 patients with preoperative DM. Of these 157 patients, 34 had IFG preoperatively. The incidence of DM or IFG was highest in the early postoperative period and decreased similar to that before surgery at 3 months postoperatively. The incidence continued to increase over the course of the study from 3 months postoperatively (Figure 2).

In the univariate analysis of factors associated with DM or IFG serially, high BMI and DP were found to be significant risk factors from 24 months postoperatively (Figure 3). The multivariate analysis revealed high BMI at 48 and 60 months postoperatively and DP at 24 and 48 months postoperatively as independent factors affecting the development of DM or IFG (Table 2).

Figure 2. Changes in endocrine function. Patients with diabetes mellitus (DM) preoperatively were excluded. IFG, impaired fasting glycemia
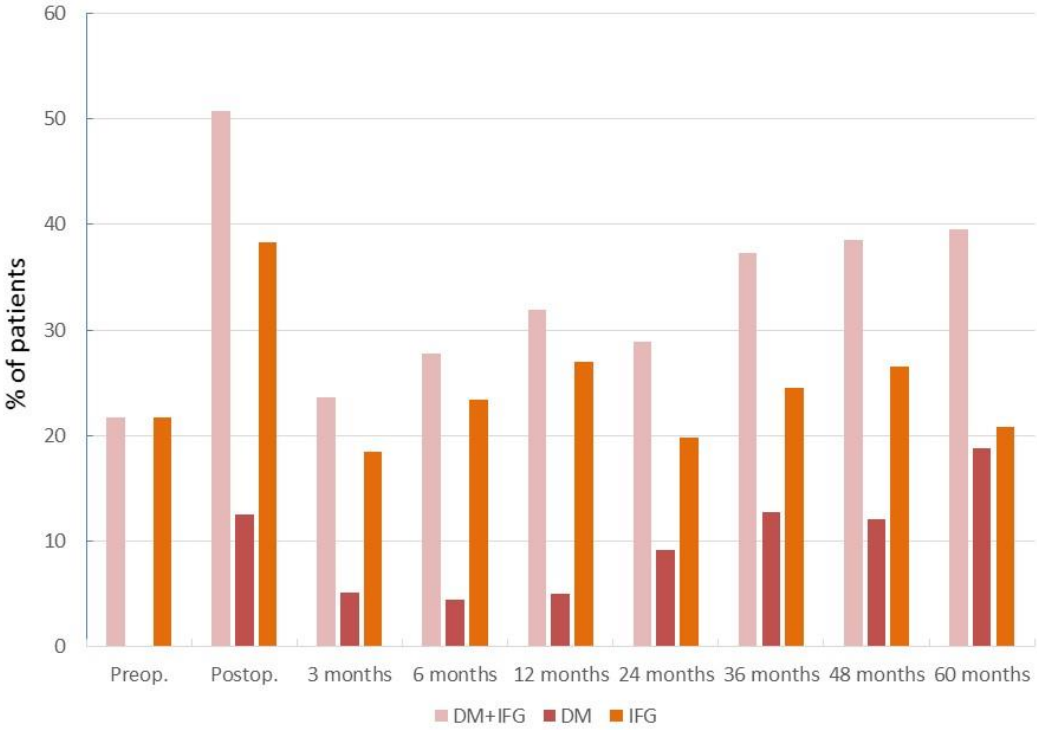
Figure 3. Changes in the incidence of DM or IFG by BMI (A), operation type (B), and adjuvant therapy (C). DM, diabetes mellitus; IFG, impaired fasting glycemia; BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy. †Significant difference in univariate analysis. ‡Independent factors in the multivariate analysis.
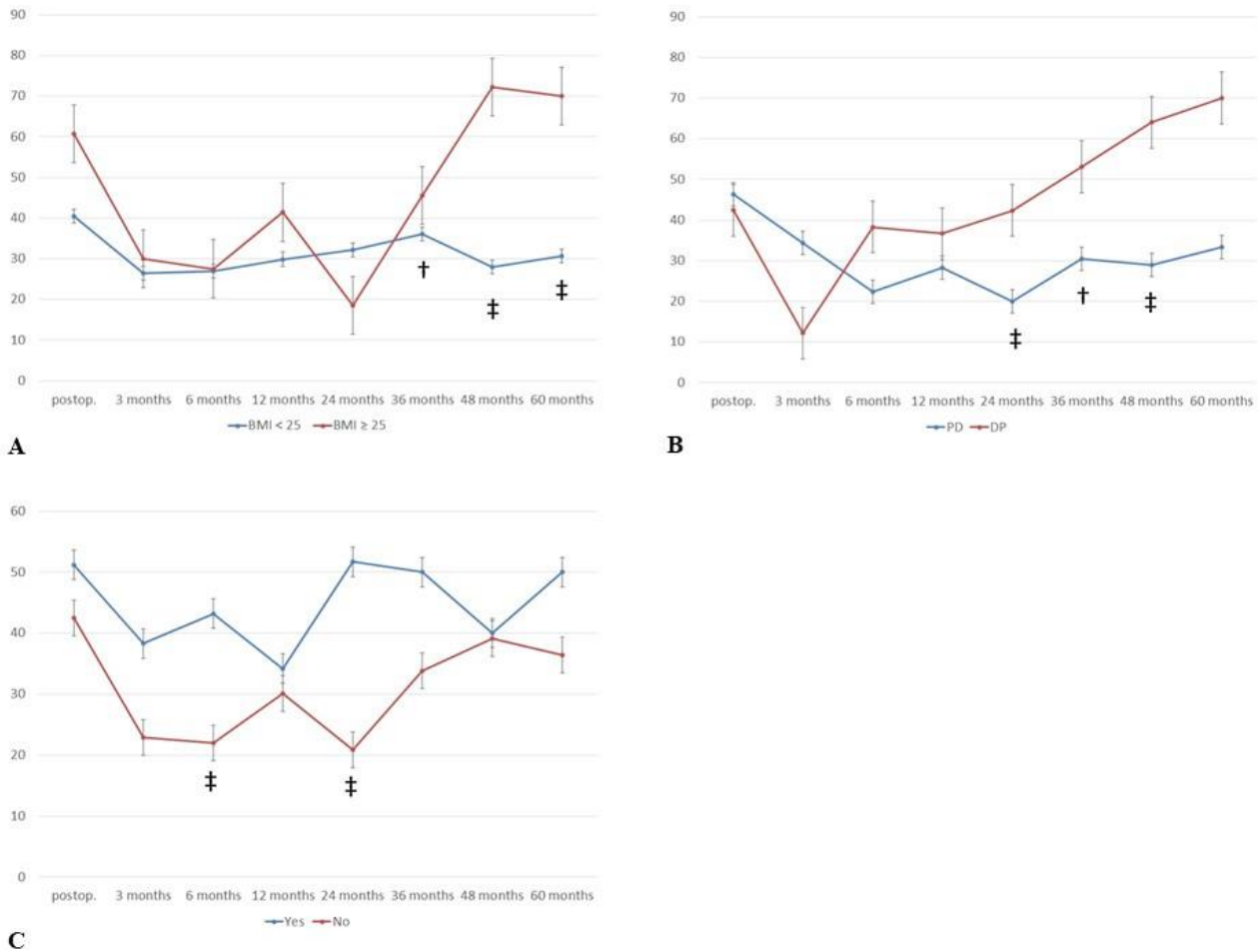
Table 2. Analysis to determine factors influencing the development of diabetes mellitus at 48 months after pancreatectomy

	No. of patients	Normal	IFG/DM	P-value	Multivariate analysis		
					Odds ratio	95% confidence interval	P-value
Age (years)				0.07	2.074	0.677–6.348	0.201
<60	36	23 (63.9%)	2 (5.6%) / 11 (30.6%)				
≥60	48	28 (58.3%)	11 (22.9%) / 9 (18.8%)				
Sex				0.498			
Male	46	26 (56.5%)	9 (19.6%) / 11 (23.9%)				
Female	38	25 (65.8%)	4 (10.5%) / 9 (23.7%)				
BMI (kg/m^2)				0.002	5.648	1.666–19.146	0.005
<25	61	44 (72.1%)	7 (11.5%) / 10 (16.4%)				
≥25	18	5 (27.8%)	5 (27.8%) / 8 (44.4%)				
Histology				0.477			
Benign	44	24 (54.5%)	8 (18.2%) / 12 (27.3%)				
Malignancy	40	27 (67.5%)	5 (12.5%) / 8 (20.0%)				
Operation type				0.006	3.675	1.244–10.859	0.019
PD	59	42 (71.2%)	8 (13.6%) / 9 (15.3%)				
DP	25	9 (36.0%)	5 (20.0%) / 11 (44.0%)				
Alcohol consumption history				0.924			
Yes	16	11 (68.8%)	2 (12.5%) / 3 (18.8%)				
No	68	40 (58.8%)	11 (16.2%) / 17 (25.0%)				
Adjuvant therapy				0.989			
Yes	20	12 (60.0%)	3 (15.0%) / 5 (25.0%)				
No	64	39 (60.9%)	10 (15.6%) / 15 (23.4%)				

IFG, impaired fasting glycemia; DM, diabetes mellitus; BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy

Exocrine function

Preoperatively, 13 (6.0%) of 217 patients had steatorrhea, and the mean diarrhea score was 28.2. Both steatorrhea (12.0%, 26 of 217) and mean diarrhea scores (63.5) were worst at the postoperative follow-up. The number of patients with steatorrhea and diarrhea decreased slowly postoperatively and returned to preoperative levels by 12 months (Figure 4A). The stool elastase level decreased postoperatively and remained low throughout the 60-month follow-up (P=0.009) (Figure 4B).

There were no significant factors associated with steatorrhea or diarrhea score. PD and adjuvant therapy were significant risk factors in the univariate analysis (Figure 5), and independent factors affecting changes in stool elastase level at almost every follow-up period from 6 months postoperatively (Table 3).

Figure 4. Changes in exocrine function: percentage of patients with steatorrhea or diarrhea (A) and mean stool elastase level (B)
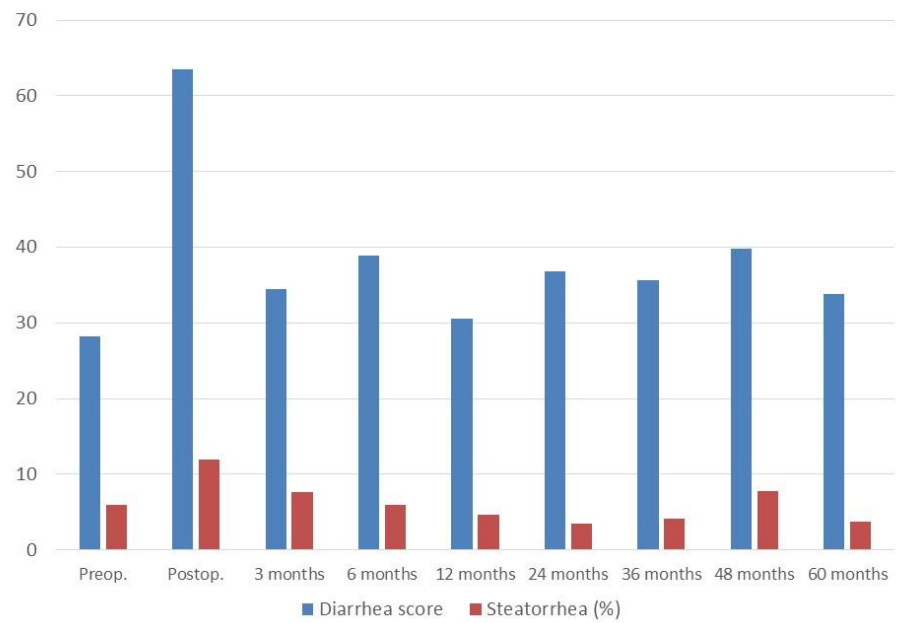
A
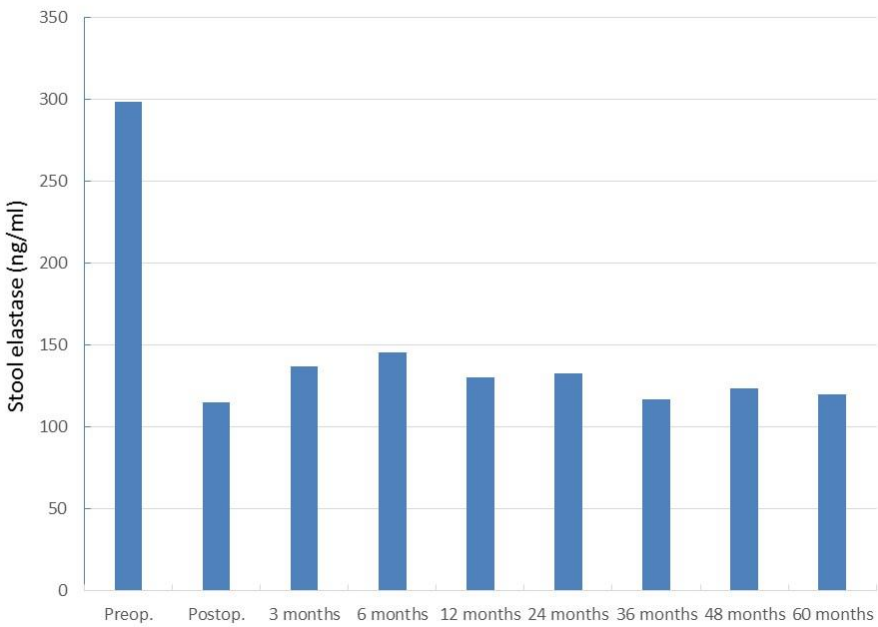
B

Figure 5. Changes in the stool elastase level by operation type (A) and adjuvant therapy (B). PD, pancreaticoduodenectomy; DP, distal pancreatectomy. ‡Independent factors in the multivariate analysis
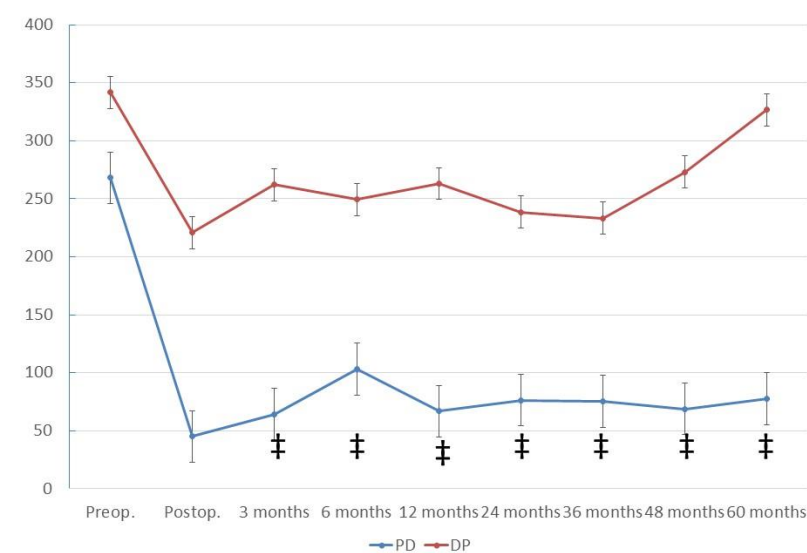
A
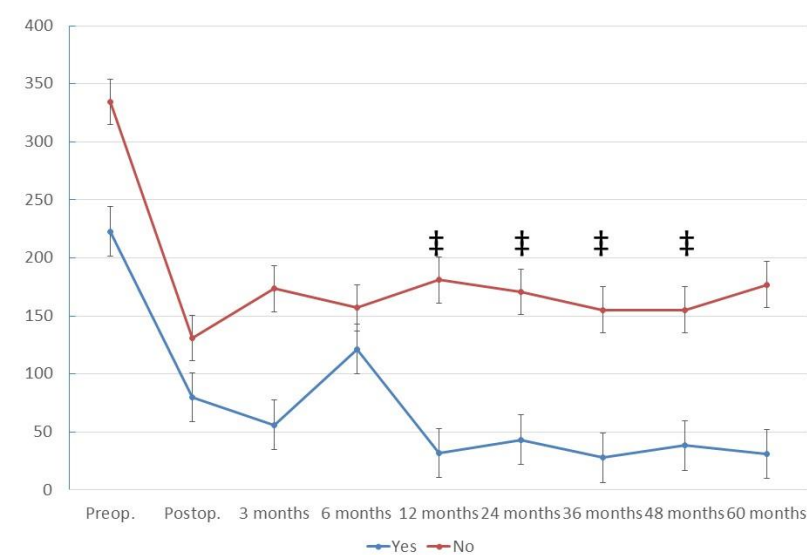
B

Table 3. Analysis to determine factors affecting the stool elastase level at 36 months after pancreatectomy

	No. of patients	Stool elastase level (ng/mL)	P-value	Multivariate analysis		
				Odds ratio	95% confidence interval	P-value
Age (years)			0.002	0.253	0.088–0.725	0.011
<60	37	175.1 (146.7)				
≥60	65	85.4 (112.6)				
Sex			0.782			
Male	58	113.6 (134.7)				
Female	45	121.0 (130.7)				
BMI (kg/m^2)			0.190			
<25	77	110.6 (125.4)				
≥25	22	153.0 (158.2)				
Histology			<0.001	0.798	0.437–1.456	0.462
Benign	43	191.5 (152.5)				
Malignant	60	63.3 (82.3)				
Operation type			<0.001	14.696	3.894–55.467	< 0.001
PD	76	75.5 (93.3)				
DP	27	233.2 (156.8)				
Alcohol consumption history			0.866			
Yes	17	112.9 (122.3)				
No	85	118.9 (135.2)				
Adjuvant therapy			<0.001	7.715	1.745–34.106	0.007
Yes	31	27.8 (44.0)				
No	72	155.2 (139.3)				

BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy

QoL

Global health status and other functional scales of the EORTC QLQ-C30 questionnaire showed similar patterns of change and scales of the EORTC QLQ-PAN26 questionnaire. Global health status decreased postoperatively and almost reached the preoperative level after 3 months (P<0.001) (Figure 6). The mean values of the dimensions of the QLQ-C30 questionnaires during follow-up are presented in Table 4. There were significant changes in the global health status and functional scales of the QLQ-C30 questionnaire during monitoring, except for the cognitive functioning scale, which showed relatively slight reduction compared to that in other scales. Regarding symptom scales in the QLQ-C30 questionnaire, significant decreases in values in several scales were found, including nausea and vomiting, pain, appetite loss, and financial difficulties. Table 5 shows the mean values for the scales of the QLQ-PAN26 questionnaire during follow-up. We found a significant reduction in hepatic and satisfaction with healthcare scales during the follow-up, while other scales did not show much changes. Although there was no significant difference between the follow-up scores, diarrhea was the only scale that did not improve throughout this study.

The results of the analysis of factors affecting scores of the questionnaires at the 6-month follow-up are reported and displayed in Tables 6–8. The female group had poorer QoL in terms of global health status (P<0.001), physical functioning (P=0.005), emotional functioning (P=0.002), social functioning (P=0.040), fatigue (P=0.013), nausea and vomiting (P=0.022), insomnia (P=0.029), and pancreatic pain (P=0.015) compared to the male group. Patients with malignant disease reported significantly lower QoL compared to patients with benign disease, which was affected by physical functioning (P=0.009), role functioning (P=0.009), social functioning (P=0.001), nausea and vomiting (P=0.007), pain (P=0.009), appetite loss (P=0.002), and sexuality (P=0.003). PD had a significantly worse effect on patients' QoL than DP, such as physical functioning (P=0.022), role functioning (P=0.007), social functioning (P=0.030), pain (P<0.001), appetite loss (P=0.031), and pancreatic pain (P=0.003). Patients who underwent adjuvant therapy also had

significantly lower QoL compared to patients who did not, in terms of physical functioning (P=0.003), role functioning (P=0.027), social functioning (P=0.042), nausea and vomiting (P=0.005), appetite loss (P=0.001), and satisfaction with healthcare (P=0.047). Global health status (P=0.020), physical functioning (P=0.009), role functioning (P=0.007), fatigue (P=0.024), nausea and vomiting (P=0.015), appetite loss (P=0.002), and financial difficulties (P=0.027) were significantly associated with exocrine insufficiency. There were no significant differences in the scores in the questionnaires between patients with and without complications, except for the emotional functioning scale (P=0.035). Female remained as an independent factor influencing QoL at 6 and 12 months after surgery on multivariate analysis (Table 9, 10).

Figure 6. Changes in quality of life (QoL): EORTC QLQ-C30 (A) and QLQ-PAN26 (B) questionnaires. Each aspect was scored on a scale from 0 to 100
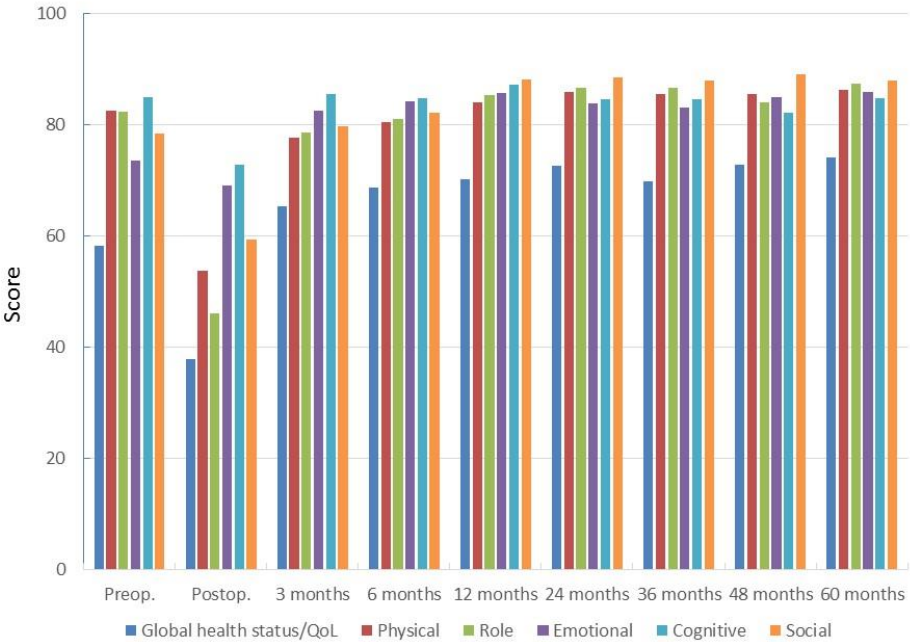
A
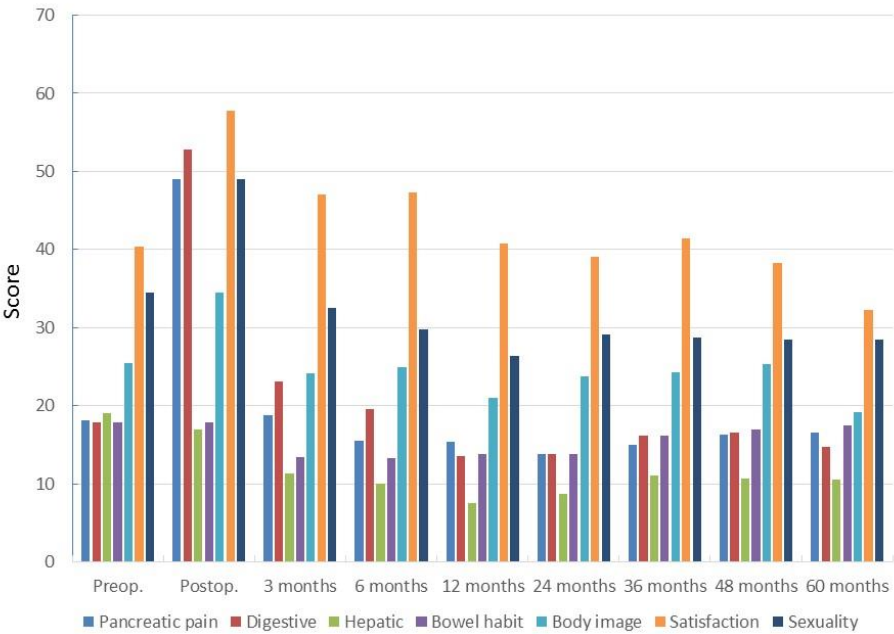
B

Table 4. Changes in the dimensions of the QLQ-C30 questionnaire during follow-up

	Preop.	6 months	12 months	24 months	36 months	48 months	60 months	*P*-value
Global health status/QoL mean (SD)	58.23 (26.43)	68.63 (21.50)	70.26 (21.74)	72.56 (18.93)	69.84 (22.19)	72.75 (20.51)	74.15 (19.30)	<0.001
Functional scales								
Physical functioning, mean (SD)	82.58 (15.43)	80.49 (13.29)	84.09 (14.56)	85.93 (12.83)	85.59 (13.64)	85.5 (14.58)	86.24 (13.31)	0.001
Role functioning, mean (SD)	82.36 (23.76)	80.94 (21.08)	85.34 (20.17)	86.61 (18.39)	86.71 (18.40)	84.05 (20.19)	87.34 (18.72)	0.042
Emotional functioning, mean (SD)	73.63 (21.27)	84.18 (17.57)	85.69 (16.43)	83.86 (15.20)	83.1 (17.77)	84.91 (16.48)	85.97 (18.80)	< 0.001
Cognitive functioning, mean (SD)	84.89 (16.49)	84.84 (14.29)	87.26 (15.12)	84.49 (13.87)	84.49 (15.22)	82.18 (15.34)	84.81 (16.49)	0.199
Social functioning, mean (SD)	78.33 (25.37)	82.18 (20.69)	88.07 (19.50)	88.54 (16.53)	87.96 (18.85)	89.08 (16.17)	88.03 (20.44)	<0.001
Symptom scales								
Fatigue, mean (SD)	28.36 (22.71)	30.68 (19.94)	25.24 (18.01)	25.56 (15.90)	27.12 (19.94)	25.86 (19.32)	24.07 (20.21)	0.061
Nausea and vomiting, mean (SD)	12.72 (21.59)	11.97 (17.81)	6.28 (13.56)	6.79 (14.55)	8.45 (16.28)	9.07 (17.38)	7.28 (14.52)	0.001
Pain, mean (SD)	24.26 (35.30)	22.45 (27.82)	17.86 (28.28)	16.57 (23.76)	15.10 (24.24)	18.91 (29.36)	16.46 (28.84)	0.037
Dyspnea, mean (SD)	31.58 (53.66)	35.11 (55.13)	22.51 (45.49)	26.01 (46.57)	27.27 (46.24)	33.62 (57.40)	27.85 (52.96)	0.238
Insomnia, mean (SD)	50.00 (77.61)	54.79 (81.62)	44.50 (70.03)	58.38 (73.94)	65.97 (77.70)	59.48 (77.99)	58.23 (84.14)	0.235
Appetite loss, mean (SD)	60.47 (82.05)	48.94 (71.27)	30.89 (60.16)	27.75 (48.63)	27.08 (58.20)	24.14 (50.43)	26.58 (47.26)	<0.001
Constipation, mean (SD)	56.14 (80.48)	46.81 (61.53)	42.63 (66.85)	47.98 (62.50)	51.39 (70.94)	49.14 (70.40)	49.37 (71.38)	0.697
Diarrhea, mean (SD)	28.24 (52.42)	38.92 (63.41)	30.53 (60.99)	36.84 (59.30)	35.66 (59.82)	39.82 (59.07)	33.77 (57.61)	0.54
Financial difficulties, mean (SD)	73.96 (89.49)	54.55 (72.72)	37.37 (62.77)	36.99 (54.09)	34.72 (55.87)	33.04 (58.82)	46.15 (73.31)	<0.001

Table 5. Changes in the dimensions of the QLQ-PAN26 questionnaire during follow-up

	Preop.	6 months	12 months	24 months	36 months	48 months	60 months	*P*-value
Pancreatic pain, mean (SD)	18.18 (20.77)	15.46 (16.13)	15.34 (18.38)	13.81 (15.12)	15.05 (15.93)	16.31 (17.11)	16.56 (19.08)	0.411
Digestive symptoms, mean (SD)	17.84 (25.79)	19.59 (21.22)	13.61 (18.60)	13.87 (19.28)	16.20 (21.04)	16.52 (24.33)	14.77 (21.01)	0.098
Hepatic, mean (SD)	19.09 (25.41)	10.02 (15.08)	7.59 (12.76)	8.67 (13.16)	11.11 (15.52)	10.63 (14.48)	10.55 (15.37)	<0.001
Altered bowel habit, mean (SD)	17.93 (21.78)	13.30 (19.96)	13.87 (20.83)	13.87 (18.42)	16.20 (19.00)	16.95 (19.16)	17.51 (21.83)	0.196
Body image, mean (SD)	25.44 (27.08)	24.91 (26.05)	21.03 (24.75)	23.74 (25.55)	24.31 (24.61)	25.29 (41.50)	19.23 (23.27)	0.507
Satisfaction with healthcare, mean (SD)	40.32 (25.24)	47.33 (29.67)	40.72 (28.86)	39.05 (30.16)	41.37 (32.06)	38.26 (28.35)	32.26 (27.83)	0.008
Sexuality, mean (SD)	34.45 (32.40)	29.72 (27.77)	26.35 (28.04)	29.17 (30.85)	28.75 (30.59)	28.42 (30.45)	28.49 (33.52)	0.439
Pancreatic pain, mean (SD)	18.18 (20.77)	15.46 (16.13)	15.34 (18.38)	13.81 (15.12)	15.05 (15.93)	16.31 (17.11)	16.56 (19.08)	0.411
Fatigue, mean (SD)	28.36 (22.71)	30.68 (19.94)	25.24 (18.01)	25.56 (15.90)	27.12 (19.94)	25.86 (19.32)	24.07 (20.21)	0.061

Table 6. Global health status / QoL and functional scales of the EORTC QLQ-C30 by demographic and clinical characteristics of patients

	Global health status/QoL	P-value	Physical functioning	P-value	Role functioning	P-value	Emotional functioning	P-value	Cognitive functioning	P-value	Social functioning	P-value
Age, mean (SD), year		0.244		0.006		0.197		0.383		0.535		0.456
< 60	70.51 (23.15)		83.19 (13.24)		82.97 (21.82)		83.03 (17.71)		85.51 (15.86)		83.33 (22.10)	
≥ 60	66.84 (19.76)		77.91 (12.87)		78.99 (20.27)		85.27 (17.44)		84.20 (12.65)		81.08 (19.29)	
Sex		<0.001		0.005		0.232		0.002		0.18		0.04
Male	73.84 (17.44)		83.04 (11.64)		82.67 (19.14)		87.93 (13.68)		86.14 (13.76)		85.15 (16.14)	
Female	62.50 (24.14)		77.54 (14.48)		78.93 (23.08)		79.82 (20.43)		83.33 (14.82)		78.74 (24.60)	
BMI (kg/m^2)		0.245		0.219		0.245		0.662		0.514		0.902
< 25	67.80 (21.26)		79.95 (13.60)		80.13 (21.09)		83.92 (17.48)		85.15 (13.86)		82.27 (19.74)	
≥ 25	72.66 (22.52)		83.13 (11.48)		84.90 (20.89)		85.42 (18.21)		83.33 (16.40)		81.77 (25.17)	
Histology		0.217		0.009		0.009		0.466		0.482		0.001
Benign	70.74 (20.56)		83.21 (12.65)		85.25 (18.92)		85.19 (14.99)		85.63 (13.00)		87.55 (16.90)	
Malignant	66.83 (22.20)		78.15 (13.44)		77.23 (22.20)		83.31 (19.55)		84.16 (15.34)		77.56 (22.54)	
Operation type		0.05		0.022		0.007		0.826		0.626		0.03
PD	66.54 (22.28)		78.99 (13.65)		78.17 (21.73)		84.37 (18.62)		84.50 (15.19)		79.97 (21.79)	
DP	73.16 (19.08)		83.77 (11.93)		87.01 (18.33)		83.76 (15.15)		85.59 (12.17)		87.01 (17.25)	
Adjuvant therapy		0.06		0.003		0.027		0.662		0.819		0.042
Yes	64.22 (21.35)		76.21 (13.57)		75.86 (20.27)		83.33 (20.91)		84.48 (15.57)		77.59 (21.07)	
No	70.61 (21.35)		82.40 (12.75)		83.21 (21.11)		84.55 (15.93)		85.00 (13.74)		84.23 (20.26)	
DM or IFG		0.546		0.112		0.431		0.321		0.27		0.387
Yes	67.53 (19.89)		78.85 (14.15)		79.55 (20.64)		85.45 (16.97)		85.98 (13.34)		80.87 (19.82)	
No	69.44 (22.93)		81.95 (12.43)		81.99 (21.52)		82.88 (18.10)		83.67 (15.05)		83.50 (21.49)	
Stool elastase level (ng/mL)		0.02		0.009		0.007		0.634		0.615		0.099
< 100	65.06 (21.36)		78.52 (13.02)		76.37 (23.21)		83.26 (19.48)		84.39 (15.64)		79.32 (22.04)	
≥ 100	74.15 (20.71)		84.76 (12.77)		86.39 (17.57)		81.75 (13.64)		85.71 (12.27)		85.71 (19.54)	
Complications		0.149		0.052		0.453		0.035		0.297		0.497
Yes	70.79 (21.32)		82.37 (11.45)		82.13 (19.28)		86.66 (16.71)		85.91 (13.89)		83.16 (21.72)	
No	66.19 (21.79)		78.53 (14.89)		79.78 (23.09)		81.21 (18.22)		83.71 (14.86)		81.09 (19.65)	

BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glycemia

Table 7. Symptom scales of the EORTC QLQ-C30 by demographic and clinical characteristics of patients

	Fatigue	P-value	N/V	P-value	Pain	P-value	Dyspnea	P-value	Insomnia	P-value	Appetite loss	P-value	Constipation	P-value	Diarrhea	P-value	Financial	P-value
Age, mean (SD), year		0.553		0.546		0.318		0.329		0.335		0.002		0.229		0.229		0.402
<60	29.79 (20.68)		12.77 (17.96)		20.38 (25.66)		39.13 (55.38)		48.91 (81.87)		32.61 (63.09)		41.30 (53.76)		44.57 (68.52)		50.00 (73.38)	
≥60	31.54 (19.27)		11.20 (17.72)		24.47 (29.78)		31.25 (54.89)		60.42 (81.41)		64.58 (75.36)		52.08 (68.02)		33.33 (57.74)		58.95 (72.19)	
Sex		0.013		0.022		0.068		0.7		0.029		0.188		0.762		0.337		0.534
Male	27.33 (17.76)		9.16 (15.30)		19.00 (24.90)		33.66 (51.53)		42.57 (72.59)		42.57 (65.34)		45.54 (60.87)		34.69 (55.80)		51.49 (67.25)	
Female	34.66 (21.71)		15.23 (19.94)		26.45 (30.52)		36.78 (59.29)		68.97 (89.33)		56.32 (77.31)		48.28 (62.62)		43.68 (71.04)		58.14 (78.91)	
BMI (kg/m^2)		0.096		0.529		0.825		0.665		0.411		0.009		0.342		0.023		0.725
<25	31.80 (20.34)		12.34 (18.51)		22.24 (27.05)		35.90 (56.74)		52.56 (81.48)		53.85 (73.95)		44.87 (60.42)		42.86 (65.54)		53.55 (69.58)	
≥25	25.35 (17.22)		10.16 (14.00)		23.44 (31.71)		31.25 (47.09)		65.63 (82.73)		25.00 (50.80)		56.25 (66.90)		19.35 (47.74)		59.38 (87.47)	
Histology		0.124		0.007		0.009		0.222		0.952		0.002		0.378		0.902		0.164
Benign	28.24 (19.81)		8.33 (12.45)		16.86 (23.78)		29.89 (48.50)		55.17 (88.60)		32.18 (60.03)		42.53 (62.19)		39.53 (59.96)		46.51 (69.79)	
Malignant	32.77 (19.91)		15.10 (20.94)		27.25 (30.17)		39.60 (60.13)		54.45 (75.53)		63.37 (77.10)		50.50 (61.03)		38.38 (66.56)		61.39 (74.79)	
Operation type		0.247		0.205		<0.001		0.627		0.95		0.031		0.544		0.463		0.12
PD	31.83 (20.72)		12.98 (19.03)		27.73 (29.64)		36.43 (55.81)		55.04 (81.93)		55.81 (75.94)		44.96 (62.45)		41.27 (67.25)		60.16 (73.54)	
DP	28.16 (18.05)		9.75 (14.69)		10.78 (18.80)		32.20 (53.95)		54.24 (81.63)		33.90 (57.57)		50.85 (59.81)		33.90 (54.49)		42.37 (69.98)	
Adjuvant therapy		0.056		0.005		0.09		0.057		0.721		0.001		0.828		0.253		0.609
Yes	34.92 (18.64)		18.10 (20.83)		27.59 (31.65)		48.28 (68.16)		51.72 (75.49)		77.59 (83.86)		48.28 (59.95)		48.21 (78.60)		58.62 (64.98)	
No	28.82 (20.28)		9.23 (15.61)		20.12 (25.69)		29.23 (47.33)		56.15 (84.45)		36.15 (61.00)		46.15 (62.45)		34.88 (55.41)		52.71 (76.11)	
DM or IFG		0.979		0.63		0.381		0.988		0.793		0.147		0.276		0.65		0.807
Yes	30.62 (19.65)		11.36 (17.33)		20.64 (27.17)		35.23 (56.81)		53.41 (80.16)		56.82 (79.94)		52.27 (60.60)		41.38 (69.13)		55.68 (74.06)	
No	30.70 (20.40)		12.63 (18.34)		24.24 (28.45)		35.35 (54.05)		56.57 (83.50)		41.41 (62.29)		42.42 (62.42)		37.11 (58.31)		53.06 (72.09)	
Stool elastase level (ng/mL)		0.024		0.015		0.066		0.572		0.852		0.002		0.938		0.212		0.027
<100	34.80 (21.80)		16.46 (21.14)		27.53 (30.90)		40.51 (58.88)		62.03 (83.67)		64.56 (75.17)		48.10 (61.73)		36.36 (662.64)		60.76 (77.49)	
≥100	26.30 (17.81)		9.18 (12.18)		17.71 (25.24)		34.69 (52.25)		59.18 (83.96)		28.57 (54.01)		48.98 (61.65)		24.49 (43.45)		33.33 (59.55)	
Complications		0.071		0.772		0.099		0.495		0.023		0.069		0.93		0.948		0.375
Yes	28.25 (17.14)		11.60 (17.70)		25.77 (27.11)		38.14 (50.92)		42.27 (74.77)		40.21 (58.91)		46.39 (64.65)		38.54 (65.49)		50.00 (72.55)	
No	33.59 (22.28)		12.36 (18.12)		18.97 (28.52)		32.58 (59.88)		69.66 (87.13)		59.55 (82.18)		47.19 (58.56)		37.93 (61.46)		59.55 (73.42)	

BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glycemia

Table 8. EORTC QLQ-PAN26 scores by demographic and clinical characteristics of patients

	Pancreatic pain	P-value	Digestive symptoms	P-value	Hepatic	P-value	Altered bowel habit	P-value	Body image	P-value	Satisfaction with healthcare	P-value	Sexuality	P-value
Age, mean (SD), year		0.247		0.806		0.018		0.017		0.545		0.069		0.174
<60	16.85 (17.77)		19.20 (23.04)		12.68 (16.46)		16.85 (21.75)		23.73 (26.52)		43.26 (29.38)		26.95 (27.20)	
≥60	14.12 (14.34)		19.97 (19.44)		7.47 (13.22)		9.90 (17.53)		26.04 (25.69)		51.27 (29.57)		33.33 (28.31)	
Sex		0.015		0.179		0.279		0.296		0.929		0.142		0.873
Male	12.71 (11.64)		17.66 (19.70)		8.91 (13.03)		11.88 (16.22)		24.75 (25.78)		50.34 (30.33)		29.41 (25.80)	
Female	18.65 (19.72)		21.84 (22.78)		11.30 (17.14)		14.94 (23.57)		25.10 (26.52)		43.85 (28.67)		30.17 (30.66)	
BMI (kg/m^2)		0.244		0.247		0.133		0.471		0.086		0.67		0.663
<25	14.83 (15.47)		20.41 (21.72)		8.97 (13.17)		12.82 (20.20)		26.39 (26.50)		46.91 (29.96)		30.20 (28.19)	
≥25	18.49 (19.02)		15.63 (18.42)		15.10 (21.73)		15.63 (18.90)		17.71 (22.77)		49.44 (28.53)		27.56 (26.22)	
Histology		0.34		0.405		0.096		0.107		0.512		0.167		0.003
Benign	14.27 (12.89)		18.20 (21.81)		8.05 (12.93)		11.69 (16.49)		23.56 (26.60)		44.05 (27.70)		22.22 (24.34)	
Malignant	16.47 (18.47)		20.79 (20.74)		11.72 (16.59)		14.69 (22.52)		26.07 (25.65)		50.17 (31.13)		36.15 (29.04)	
Operation type		0.003		0.51		0.54		0.291		0.154		0.323		0.249
PD	17.48 (17.42)		20.28 (19.76)		9.56 (15.70)		14.34 (20.28)		26.74 (26.88)		45.87 (30.43)		31.60 (28.46)	
DP	11.02 (11.83)		18.08 (24.23)		11.02 (13.71)		11.02 (19.23)		20.90 (23.89)		50.60 (27.88)		25.89 (26.19)	
Adjuvant therapy		0.657		0.224		0.981		0.158		0.149		0.047		0.134
Yes	16.33 (19.35)		22.41 (22.20)		10.06 (14.62)		16.95 (26.03)		29.02 (28.19)		53.87 (31.30)		34.78 (29.15)	
No	15.06 (14.53		18.33 (20.74)		10.00(15.33)		11.67 (16.43)		23.08 (24.94)		44.40 (28.55)		27.32 (26.92)	
DM or IFG		0.342		0.017		0.138		0.864		0.14		0.147		0.081
Yes	14.30 (16.37)		23.67 (24.07)		8.33 (13.61)		13.64 (21.52)		28.03 (26.69)		50.58 (28.52)		34.36 (29.15)	
No	16.55 (15.98)		16.16 (17.73)		11.62 (16.23)		13.13 (18.64)		22.39 (25.33)		44.15 (30.60)		26.19 (26.13)	
Stool elastase level (ng/mL)		0.463		0.318		0.574		0.605		0.219		0.548		0.839
<100	16.14 (16.63)		20.68 (19.47)		9.70 (15.47)		11.60 (16.95)		28.06 (28.31)		43.72 (30.83)		27.32 (25.28)	
≥100	14.12 (12.29)		17.01 (21.11)		11.22 (13.77)		13.27 (18.63)		22.11 (23.17)		47.10 (28.83)		28.38 (24.17)	
Complications		0.995		0.893		0.081		0.122		0.05		0.403		0.633
Yes	15.44 (14.32)		19.24 (19.15)		8.08 (12.29)		10.82 (16.50)		21.13 (24.71)		49.28 (30.68)		28.51 (27.05)	
No	15.45 (18.10)		19.66 (23.38)		11.99 (17.41)		15.36 (22.50)		28.65 (27.18)		45.54 (28.86)		30.77 (29.05)	

BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glycemia

Table 9. Predictor variables for global health status / QoL at 6 months after surgery

| | Score (SD) | p-value | Odds Ratio | 95% confidence interval | | p-value |
				Lower	Upper	
Age (year)		0.244				
≥ 60	70.51 (23.15)					
< 60	66.84 (19.76)					
Gender		<0.001	0.371	0.170	0.809	0.013
Male	73.84 (17.44)					
Female	62.50 (24.14)					
BMI (kg/m²)		0.245				
< 25	67.80 (21.26)					
≥ 25	72.66 (22.52)					
Histology		0.217				
Benign	70.74 (20.56)					
Malignant	66.83 (22.20)					
Operation type		0.05	1.290	0.424	3.924	0.654
PD	66.54 (22.28)					
DP	73.16 (19.08)					
Adjuvant therapy		0.06	1.411	0.583	3.414	0.445
Yes	64.22 (21.35)					
No	70.61 (21.35)					
DM or IFG		0.546				
Yes	67.53 (19.89)					
No	69.44 (22.93)					
Stool elastase level (ng/mL)		0.02	0.459	0.721	6.404	0.170
< 100	65.06 (21.36)					
≥ 100	74.15 (20.71)					
Complications		0.149				
Yes	70.79 (21.32)					
No	66.19 (21.79)					

SD, standard deviation; BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glucose

Table 10. Predictor variables for global health status / QoL at 12 months after surgery

| | Score (SD) | p-value | Odds Ratio | 95% confidence interval | | p-value |
				Lower	Upper	
Age (year)		0.664				
≥ 60	70.96 (18.25)					
< 60	69.57 (25.09)					
Gender		0.003	0.449	0.246	0.821	0.009
Male	74.67 (18.85)					
Female	65.26 (23.74)					
BMI (kg/m^2)		0.346				
< 25	69.24 (22.34)					
≥ 25	73.23 (20.17)					
Histology		0.270				
Benign	72.22 (20.55)					
Malignant	68.71 (22.62)					
Operation type		0.082	1.780	0.927	3.419	0.083
PD	68.40 (22.51)					
DP	74.31 (19.55)					
Adjuvant therapy		0.473				
Yes	68.65 (21.73)					
No	71.06 (21.79)					
DM or IFG		0.325				
Yes	68.71 (22.77)					
No	71.85 (20.78)					
Stool elastase level (ng/mL)		0.328				
< 100	69.28 (22.62)					
≥ 100	73.13 (20.50)					
Complications		0.141	1.636	0.843	3.174	0.146
Yes	72.63 (19.44)					
No	67.92 (23.95)					

SD, standard deviation; BMI, body mass index; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glucose

Subgroup analysis

Classification by operation type

A total of 148 patients (68.2%) underwent PD (PD group) and 69 (31.8%) underwent DP (DP group). RBW, BMI, and TSFT of both groups continued to decrease postoperatively but began to increase after 6 months, as in all patients, although the DP group maintained higher values than the PD group during the entire follow-up period (Figure 7A). Biochemical parameters, including transferrin, albumin, and protein levels, recovered to the preoperative level after 3 months and showed similar patterns of change in both groups (Figure 7B). Incidence of DM or IFG after surgery was significantly higher in the DP group than in the PD group and DP was an independent factor affecting the development of DM or IFG (Figure 8). The stool elastase level in the PD group decreased to severe pancreatic exocrine insufficiency (PEI) after surgery, and did not recover during the follow-up period (Figure 9). PD was an independent factor affecting changes in stool elastase level at almost every follow-up period from 6 months postoperatively (Table 3). Global health status and other functional scales of the EORTC QLQ-C30 questionnaire showed relatively higher scores in the DP group than in the PD group (Figure 10A). There were significant differences in the global health status between the two groups at 6 months postoperatively, but, the operation type was not independent risk factor in multivariate analysis (Table 9). The scales of the QLQ-PAN26 questionnaire showed similar patterns of change in both groups (Figure 10B).

Figure 7. Changes in nutritional status by operation type: physical parameters (A) and biochemical parameters (B). PD, pancreaticoduodenectomy; DP, distal pancreatectomy; RBW, relative body weight; TSFT, triceps skinfold thickness; BMI, body mass index
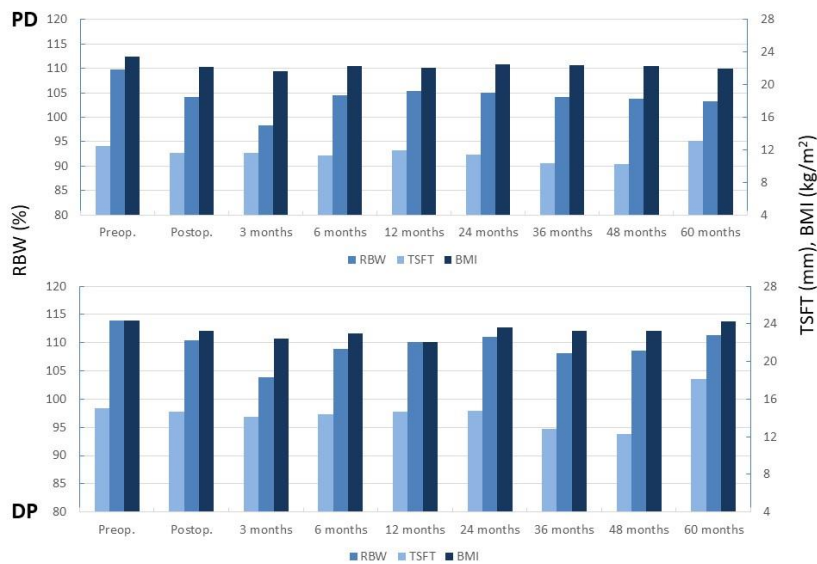
A
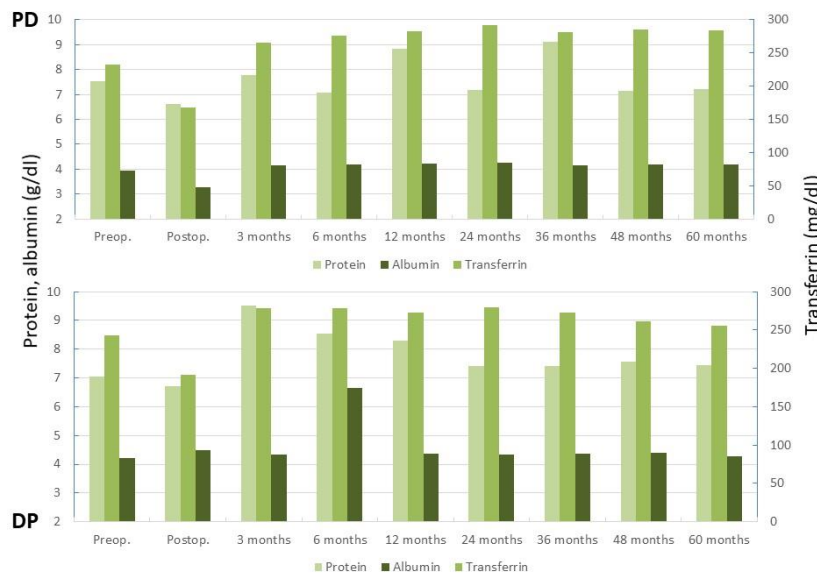
B

Figure 8. Changes in endocrine function by operation type. Incidence of DM or IFG after surgery was significantly higher in the DP group than in the PD group and DP was an independent factor affecting the development of DM or IFG. PD, pancreaticoduodenectomy; DP, distal pancreatectomy; DM, diabetes mellitus; IFG, impaired fasting glycemia
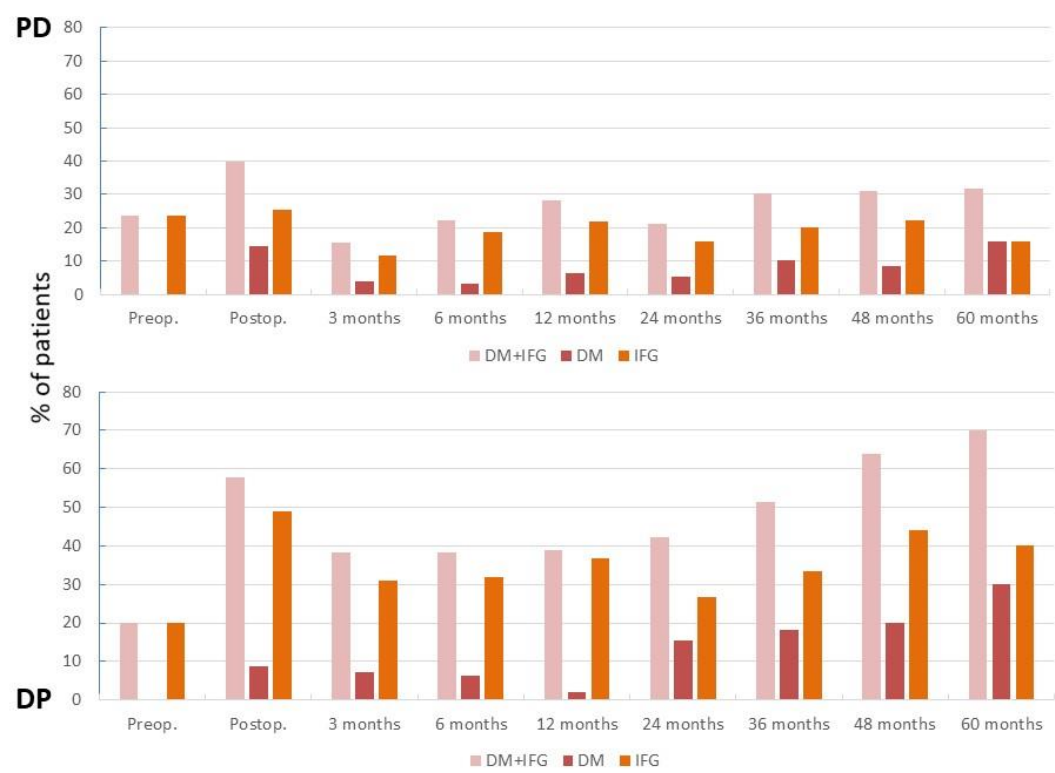
Figure 9. Changes in mean stool elastase level by operation type. The stool elastase level in the PD group decreased to severe pancreatic exocrine insufficiency after surgery and did not recover during the follow-up period. PD, pancreaticoduodenectomy; DP, distal pancreatectomy
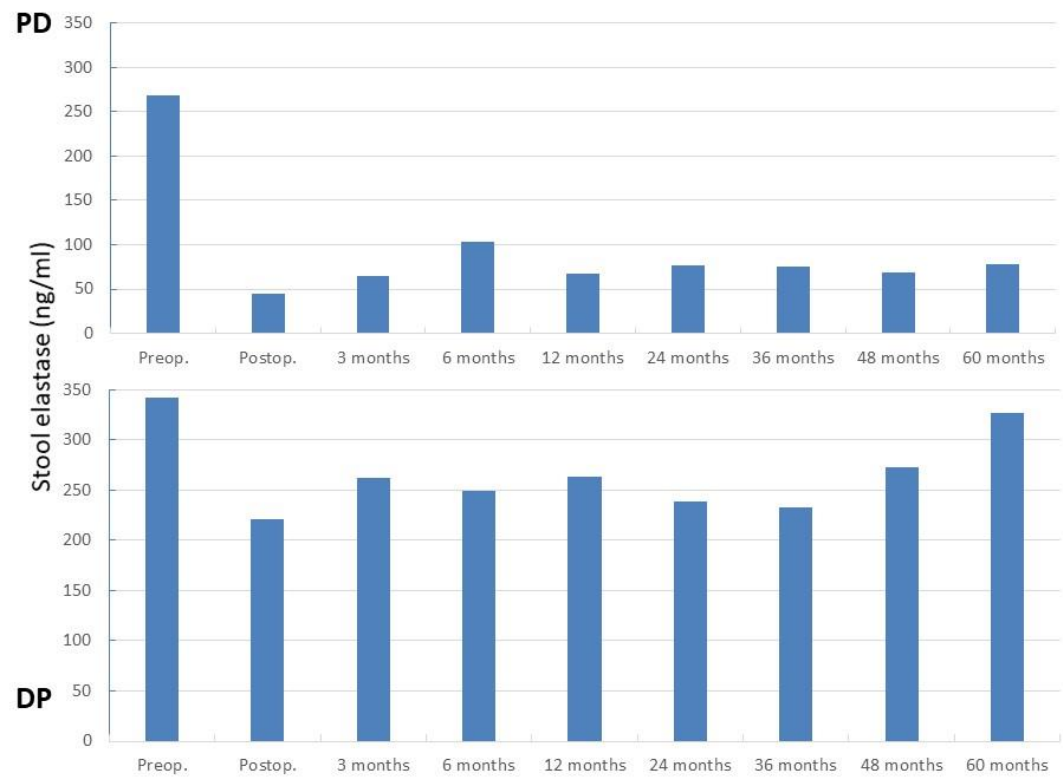
Figure 10. Changes in quality of life by operation type: EORTC QLQ-C30 (A) and QLQ-PAN26 (B) questionnaires. Each aspect was scored on a scale from 0 to 100. PD, pancreaticoduodenectomy; DP, distal pancreatectomy


A

B
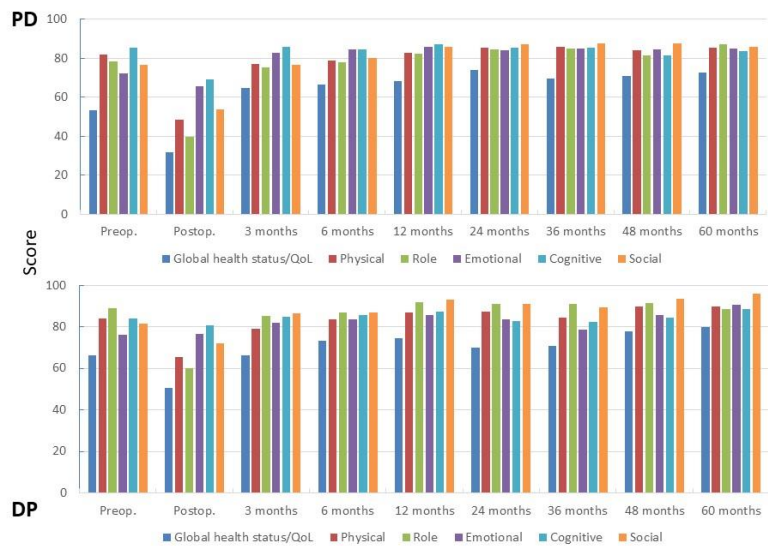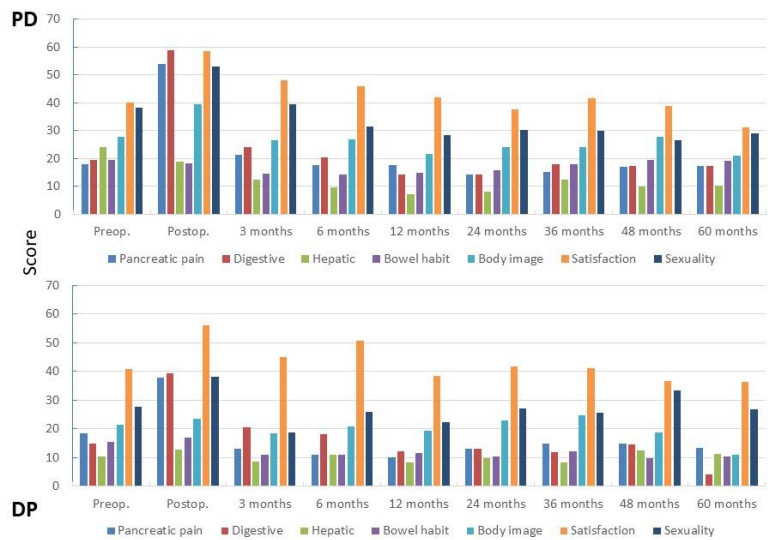
Classification by histology

About 40-45% of all enrolled patients were benign (benign group) and about 55-60% were malignant (malignant group). Physical parameters and biochemical parameters showed similar patterns of change in both groups (Figure 11). There was no significant difference between the two groups in the incidence of newly developed DM or IFG after surgery during the follow-up period (Figure 12). Although there was a significant difference in mean stool elastase levels between the two groups from 12 months after surgery to the end of follow-up, in multivariate analysis, histology was not an independent risk factor for PEI (Figure 13). The QoL questionnaire scores by EORTC QLQ-C30 and QLQ-PAN26 showed similar patterns of change between the two groups (Figure 14).

Figure 11. Changes in nutritional status by histology: physical parameters (A) and biochemical parameters (B). RBW, relative body weight; TSFT, triceps skinfold thickness; BMI, body mass index
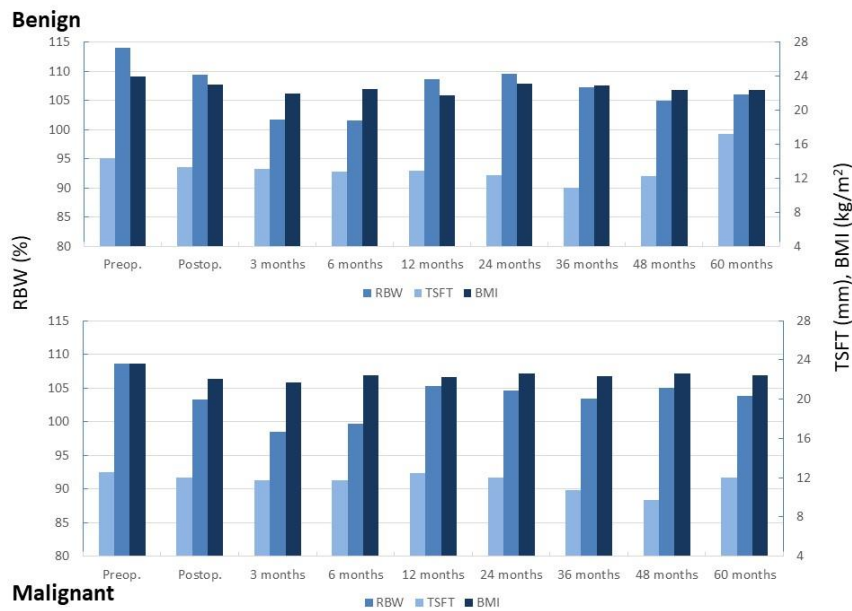
A
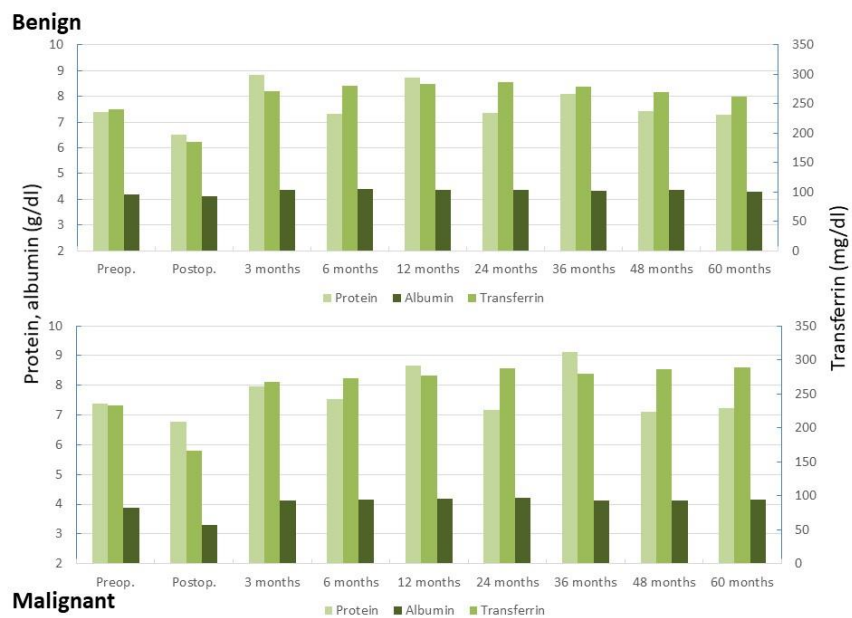
B

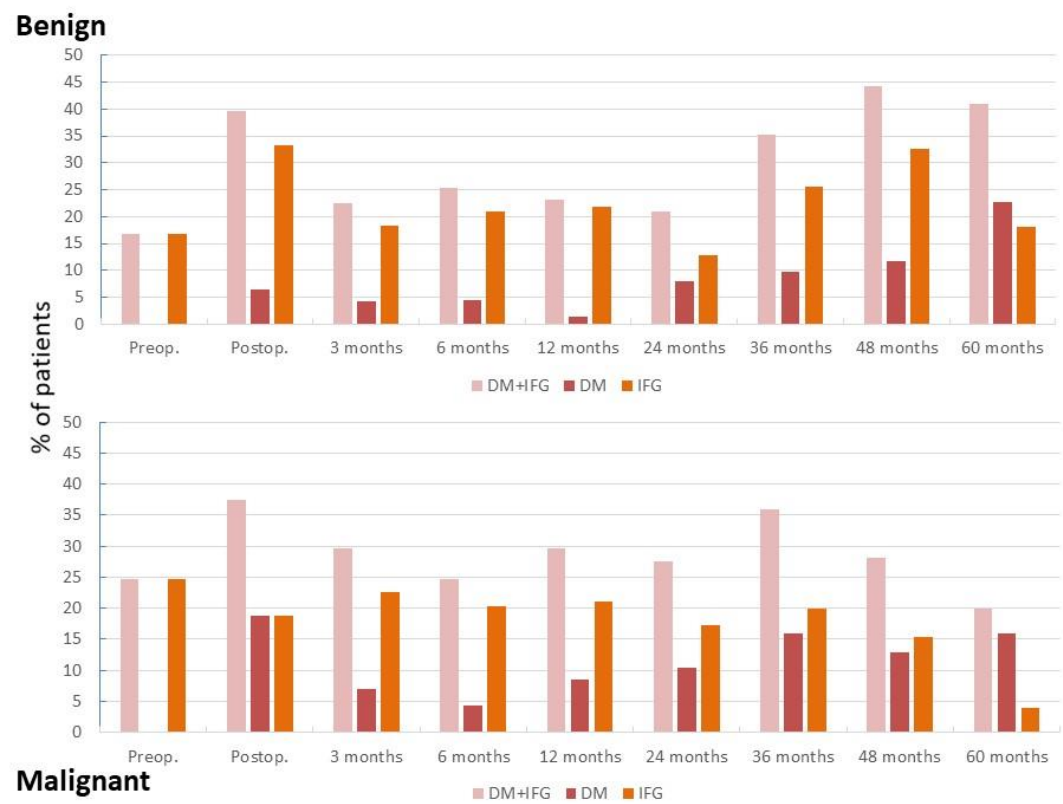Figure 12. Changes in endocrine function by histology. DM, diabetes mellitus; IFG, impaired fasting glycemia

Figure 13. Changes in the stool elastase level by histology. Although there was a significant difference in mean stool elastase levels between the two groups from 12 months after surgery to the end of follow-up, in multivariate analysis, histology was not an independent risk factor for pancreatic exocrine insufficiency. † Significant difference in univariate analysis.
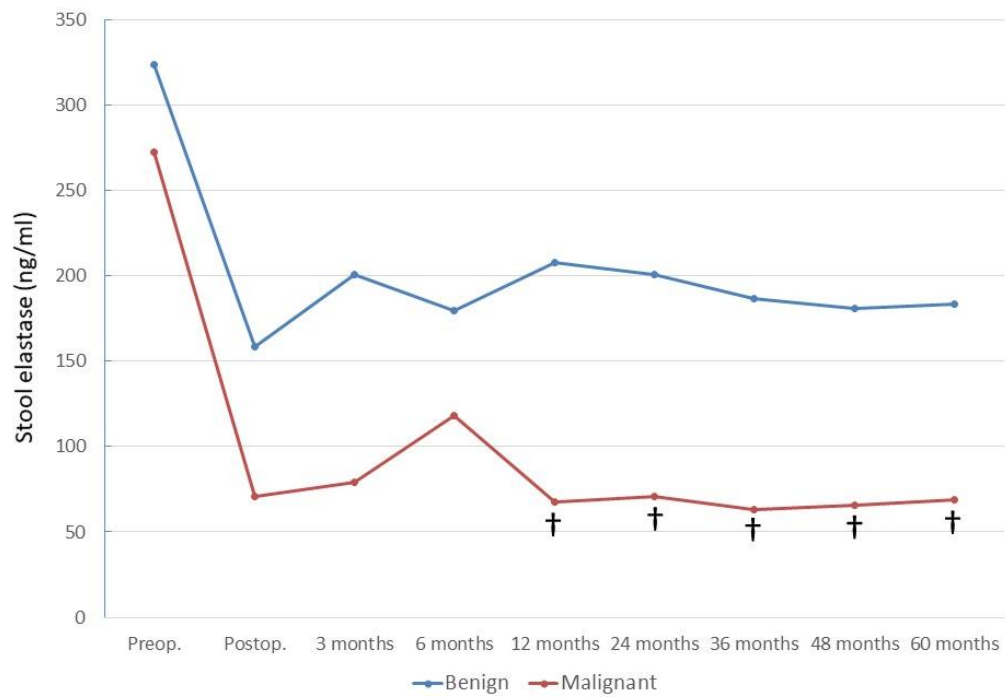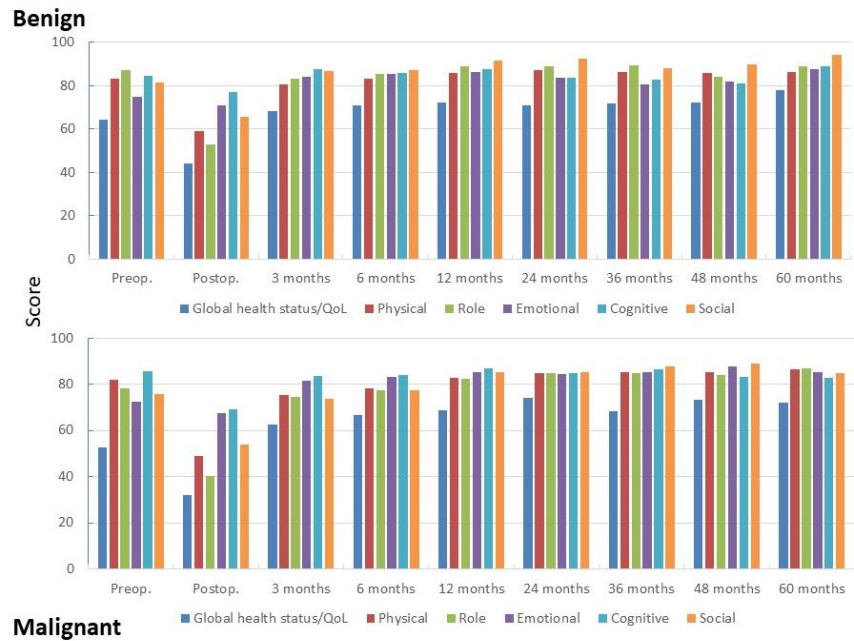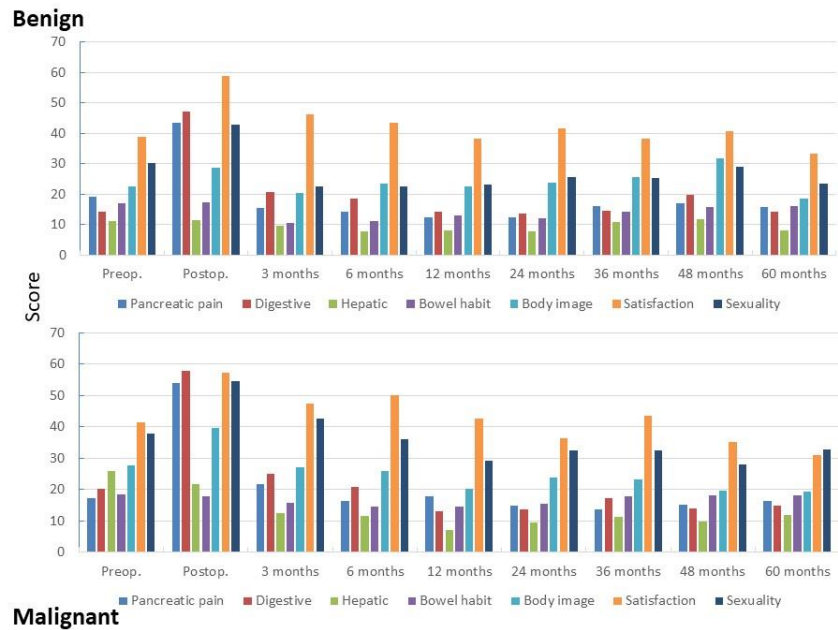
Figure 14. Changes in quality of life by histology: EORTC QLQ-C30 (A) and QLQ-PAN26 (B) questionnaires. Each aspect was scored on a scale from 0 to 100.


A

B

Classification by gender

RBW, TSFT, and BMI showed similar patterns of change between male and female patients (Figure 15A). Biochemical parameters recovered to preoperative values 3 months after surgery in both groups (Figure 15B). There was no significant difference in the incidence of DM or IFG between men and women during the follow-up period except for 6 months after surgery (Figure 16). Stool elastase levels showed similar patterns in the two groups from 12 months after surgery (Figure 17). Male patients scored relatively higher than female patients on the EORTC QLQ-C30 questionnaire (Figure 18A). There was a significant difference in global health status / QoL between the two groups at 6 and 12 months after surgery and female gender was an independent risk factor for low global health status / QoL in a multivariate analysis (Table 9, 10). In EORTC QLQ-PAN26 questionnaire, female patients showed a relatively slow decrease in symptom scale scores than male patients (Figure 18B).

Figure 15. Changes in nutritional status by gender: physical parameters (A) and biochemical parameters (B). RBW, relative body weight; TSFT, triceps skinfold thickness; BMI, body mass index
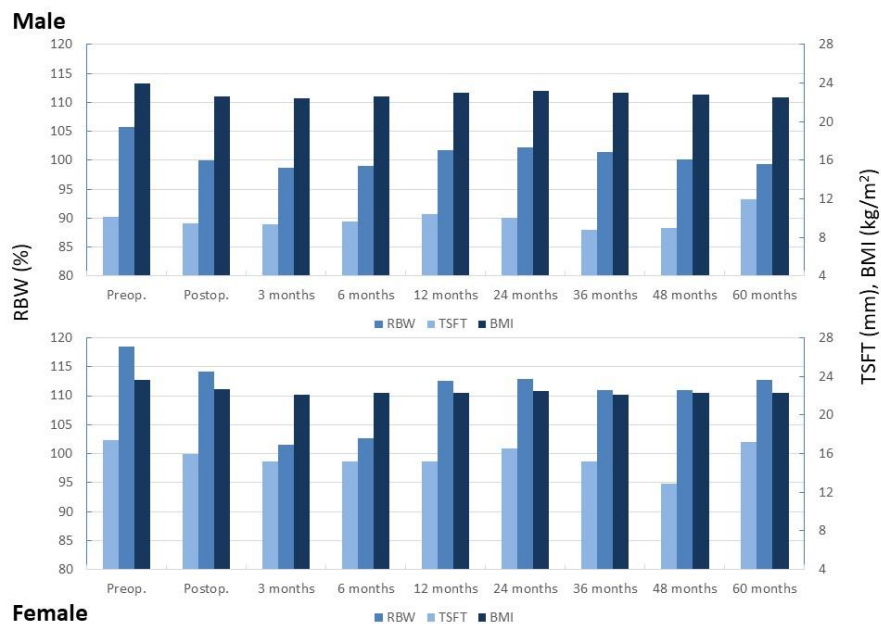
A
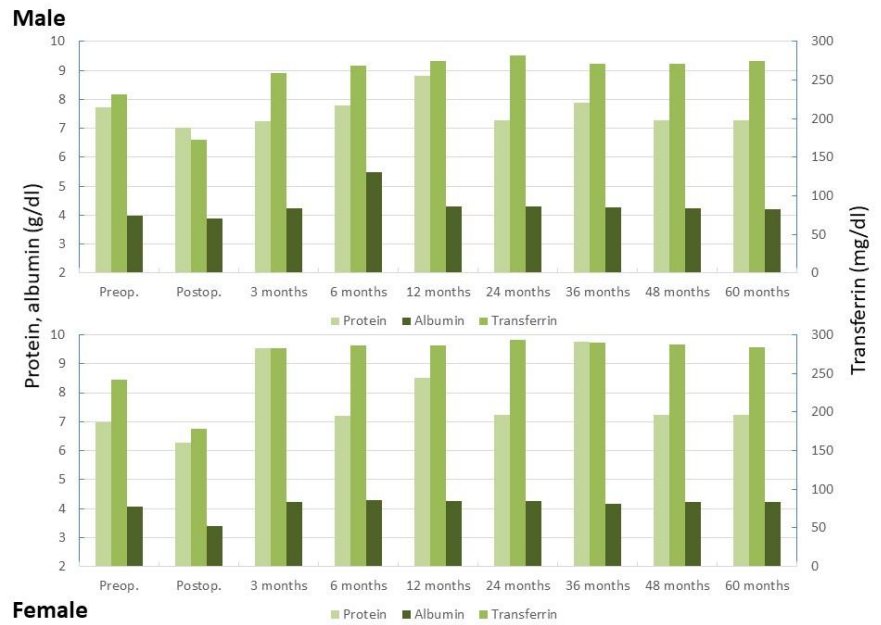
B

Figure 16. Changes in the incidence of DM or IFG by gender. ‡ Independent factor in the

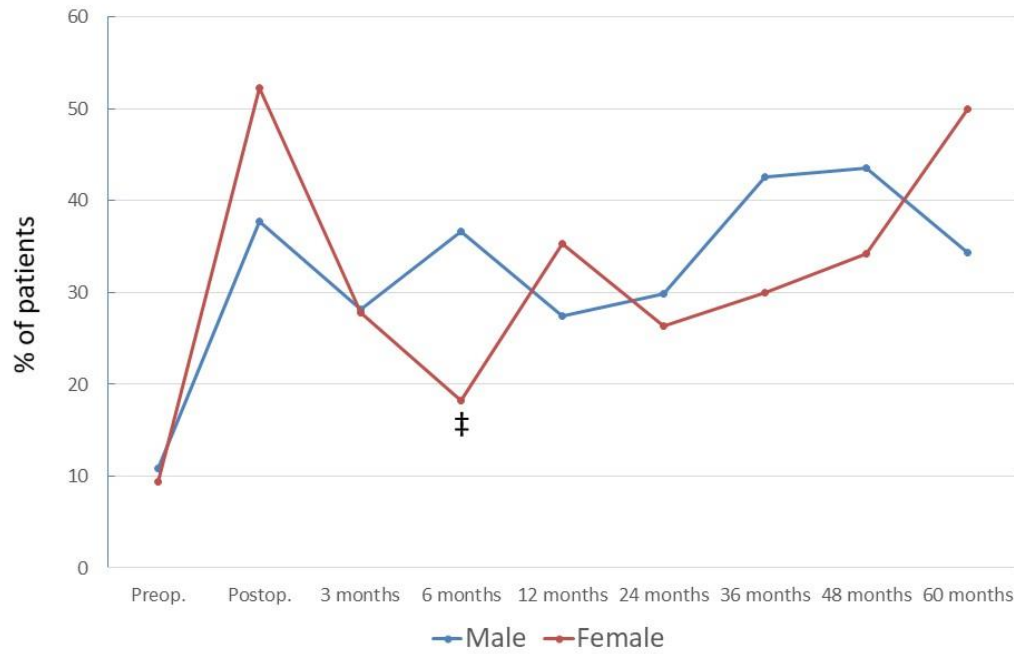multivariate analysis. DM, diabetes mellitus; IFG, impaired fasting glycemia

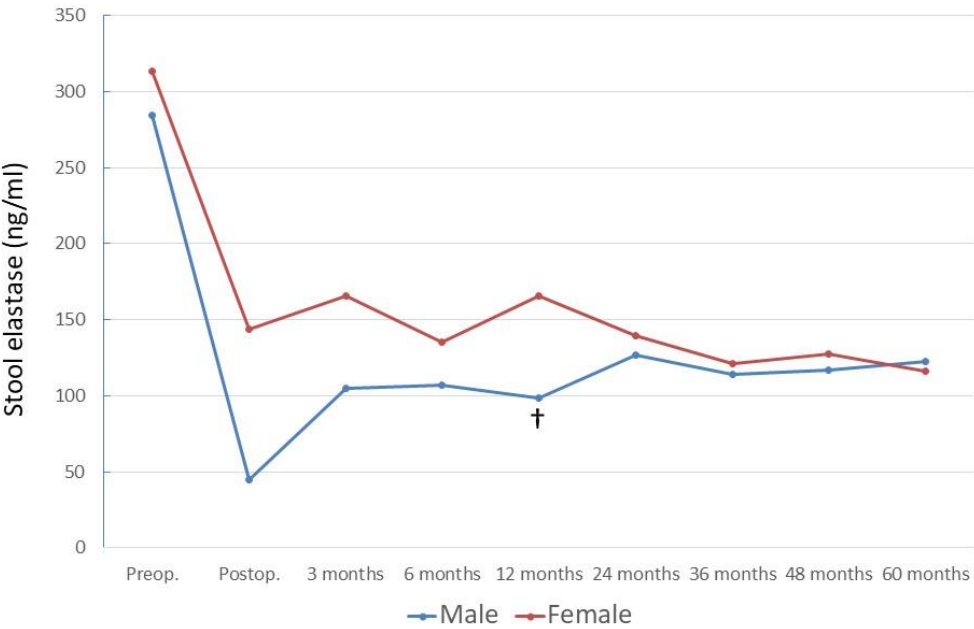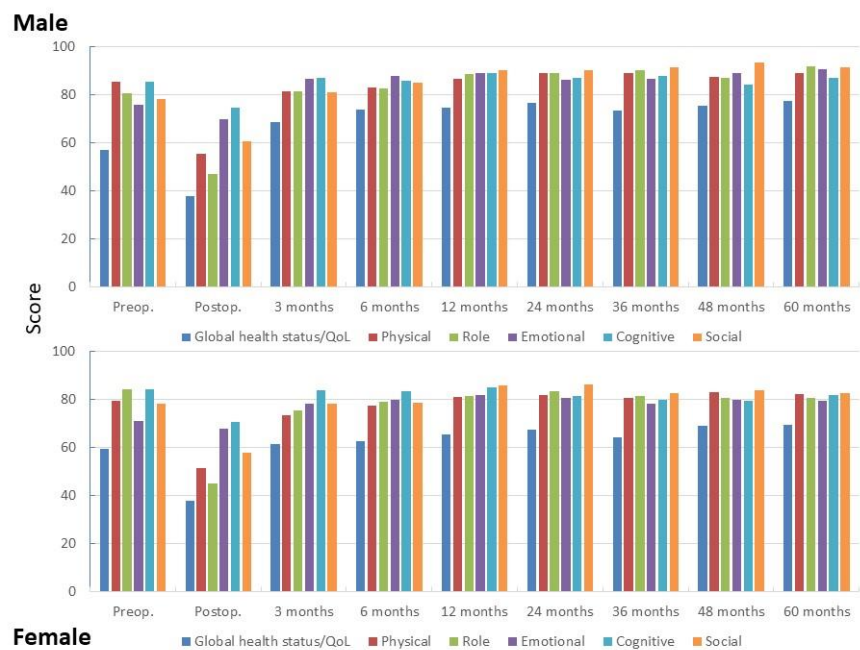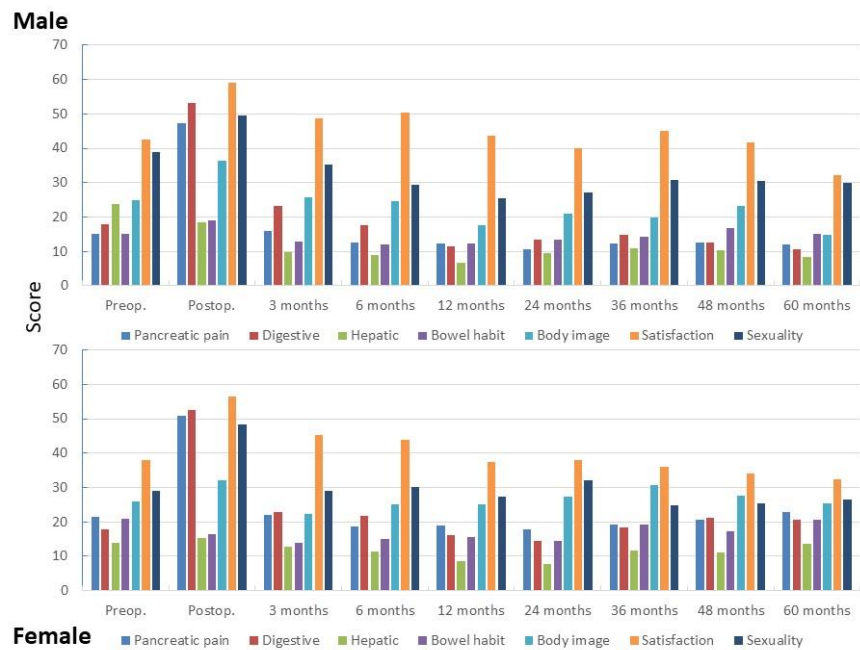Figure 17. Changes in the stool elastase level by gender. † Significant difference in univariate analysis.

Figure 18. Changes in quality of life by gender: EORTC QLQ-C30 (A) and QLQ-PAN26 (B) questionnaires. Each aspect was scored on a scale from 0 to 100.

A

B

Discussion

This is the first prospective study to assess serial changes in pancreatic function and QoL based on consecutive and regular follow-up data at 5 years after pancreatectomy. As an extension of our earlier study, which evaluated pancreatic function and QoL of patients after pancreatectomy for 1 year[22], the present study included more patients and extended the follow-up period to 5 years to assess the impact of deterioration of pancreatic function after pancreatectomy on QoL of patients. A previous study reported that approximately half of patients are expected to recover from pancreatectomy in terms of pancreatic function and QoL after 6 months, and most patients have some measurable degree of functional impairment after this type of surgery, although situations requiring clinical treatment are uncommon. In an effort to identify patients with impaired pancreatic function or QoL as early as possible, most surgeons in Korea follow patients in outpatient clinics at intervals of <6 months for at least 5 years after pancreatectomy. Through this, they found that changes in the pancreatic function and QoL of patients continue to progress >1 year postoperatively.

Even after our previous study, few studies have evaluated pancreatic function and QoL after pancreatectomy in a specific setting. Heerkens et al. reported no statistically significant and clinically relevant differences between patients with and without severe complications in QoL up to 12 months postoperatively[23,24]. Eaton et al. found that pancreatic complications were associated with impaired QoL in several domains during the early postoperative period[25]. However, these studies focused on the relationship between complications and QoL of patients and did not describe any changes in symptoms, pancreatic function, and QoL.

Malnutrition can impact disease progression and survival in cancer patients. Substantial studies have shown that weight loss in cancer is associated with poor prognosis, poor QoL, lower activity level, increased treatment-related adverse symptoms, and reduced tumor response to therapy[26]. Geng et al. reported that prognostic nutritional index (PNI) not only correlated with shorter overall

42

survival (OS), but PNI was also identified as an independent prognostic factor for OS in patients with advanced pancreatic cancer[27]. A retrospective study on patients who underwent resection for pancreatic cancer found that the PNI is associated with overall survival and postoperative complications, in particular pancreatic fistula[28]. In a study to reevaluate the factors responsible for hospital morbidity, mortality and post-operative survival following pancreaticoduodenectomy for ampullary cancer, pre-operative nutritional support and careful surgical technique to prevent post-operative sepsis are mandatory to reduce operative morbidity and mortality[29]. In the present study, almost all patients had weight loss, nutritional impairment, impaired pancreatic function, and declined QoL. However, nutritional status and biochemical parameters recovered rapidly after 3-month follow-up. Biochemical parameters, such as transferrin, albumin, and protein levels, had recovered to the preoperative level after 3 months.

After excluding patients with preoperative DM, serial assessment of endocrine function of the pancreas showed postoperative deterioration in more than half of patients (DM, 12.5%; IFG, 38.3%) and a pattern of recovery at 3 months. Although patients aged ≥60 years had relatively higher rates of impaired glucose tolerance than patients aged <60 years throughout the follow-up, in the present study, old age was not a significant risk factor for DM or IFG, unlike in the previous study. After 6 months, endocrine function continued to decrease, especially in patients with high BMI or those who underwent DP since the 24-month follow-up. High BMI is a well-known risk factor for DM. Wu et al. found through a systemic review that the incidence of new-onset DM was significantly different between different types of resection from 9% to 24% after PD (pooled estimate, 16%; 95% confidence interval (CI), 14%–17%) and 3%–40% after DP (pooled estimate, 21%; 95% CI, 16%–25%)[30]. In a study to investigate the postoperative   -cell function (BCF) and hormonal responses of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide after PD and DP, the authors showed an increased GLP-1 level after DP, which might reflect the relatively insufficient BCF[31]. This may explain why DP was one of the independent risk factors associated with endocrine insufficiency of the pancreas in this study.

Careful follow-up focusing specifically on the development of DM in patients with risk factors seems prudent.

The stool elastase assay is the most widely used method for diagnosing pancreatic exocrine insufficiency (PEI). This test is a simple and accurate functional test for PEI, and it is hardly influenced by extrapancreatic disorders or therapy with exogenous enzymes[32]. In a systematic review and meta-analysis of studies that compared fecal level of elastase-1 for detection of PEI, the authors concluded that it is helpful to select the actual pancreatic enzyme replacement therapy (PERT) target in the high pre-test probability group[33].

Both steatorrhea and diarrhea score had returned to preoperative levels by 12 months, although the diarrhea score never recovered below the preoperative values throughout the study. The mean diarrhea scores were higher in the PD group than in the DP group and in the group with a stool elastase level <100 ng/mL, but the difference was not statistically significant. The mean stool elastase level of all patients did not recover postoperatively throughout this study. However, according to the type of operation, a risk factor affecting changes in stool elastase level, the PD group showed severe PEI postoperatively, while the DP group maintained the stool elastase level more than the upper limit of mild PEI after surgery. PEI after pancreatectomy can result in nutritional imbalance and weight loss[34]. In the per-protocol analysis of a randomized trial to evaluate the effects of PERT after PD, patients in the PERT group gained a mean of 1.09 kg in weight and patients in the placebo group lost a mean of 2.28 kg (difference between groups, 3.37 kg; P < 0.001)[35]. The authors of this study reported that PERT could increase the body weight and nutritional parameters with active education and monitoring.

A univariate analysis at 6 months, when global health status/QoL and other functional scales nearly recovered to preoperative levels, showed that global health status/QoL and other functional scales were significantly influenced by many demographic and clinical findings, including malignancy, type of operation, adjuvant therapy, and severe exocrine pancreatic insufficiency (Supplementary Table 3). In the subgroup analysis by gender, male patients scored relatively

higher than female patients on the EORTC QLQ-C30 questionnaire. There was a significant difference in global health status / QoL between the two groups at 6 and 12 months after surgery and female gender was an independent risk factor for low global health status / QoL in a multivariate analysis. All scales of the QoL questionnaires improved from preoperative levels at 12 months postoperatively, except for the diarrhea scale, which did not recover throughout the study. Particularly, the scores of global health status/QoL and other functional scales at this time were relatively higher than the preoperative levels, and there was no significant difference compared with scores for the general population[36,37]. Therefore, the postoperative 12 months can be evaluated as the time when patients who underwent pancreatectomy can fully return to their daily lives.

Patients who have undergone pancreatectomy have a high mortality rate postoperatively and poor overall condition, requiring a large number of patients for a long-term follow-up study. The cohort of 217 patients in this study represents the largest number of such patients studied serially with respect to the relationship between pancreatic function and QoL reported to date, which makes this study extremely valuable and important. One of the limitations of this study was the reduction in the number of follow-up patients due to several exclusion criteria in 60 months. However, because the distribution of demographic and clinical characteristics did not significantly differ between each follow-up period, it is thought that there would be no associated bias in the comparative analysis between each follow-up period. As a second limitation, the present study only included patients enrolled from a single center in Korea. Thus, the results of this study are difficult to apply directly to the entire Korean and Western populations, which have different cultural ethnic factors. However, this study can provide basic information on the concern of many surgeons by using QoL questionnaires to understand not only the pancreatic function but also the physical and mental statuses in patients undergoing pancreatic resection for a long period of 5 years.

Therefore, incorporating both preoperative and serial postoperative QoL assessments, the current study substantially adds to the literature on QoL after pancreatectomy. In the serial follow-up of patients after pancreatectomy, the rate of patients with exocrine or endocrine pancreatic insufficiency increases gradually, although their QoL improved after 3 months postoperatively. Particularly, there are many risk factors that affect pancreatic function and QoL, such as type of operation, malignancy, and adjuvant therapy. The surgeon should consider these factors during the serial follow-up of patients after pancreatectomy.

Reference

1. Cameron JL, Riall TS, Coleman J, Belcher K. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006;244:10-5.

2. Cohen JR, Kuchta N, Geller N, Shires GT, Dineen P. Pancreaticoduodenectomy for benign disease. Ann Surg. 1983;197:68–71.

3. Herter FP, Cooperman AM, Ahlborn TN, Antinori C. Surgical experience with pancreatic and periampullary cancer. Ann Surg. 1982;195:274-81.

4. Michelassi F, Erroi F, Dawson PJ, Pietrabissa A, Noda S, Handcock M, et al. Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg. 1989;210:544-54.

5. Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann Surg. 1998;228:685-91.

6. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s – pathology, complications, and outcomes. Ann Surg. 1997;226:248-57.

7. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg. 2000;231:890-8.

8. Jalleh RP, Williamson RC. Pancreatic exocrine and endocrine function after operations for chronic-pancreatitis. Ann Surg. 1992;216:656-62.

9. Klempa I, Spatny M, Menzel J, Baca I, Nustede R, Stöckmann F, et al. Pancreatic function and quality of life after resection of the head of the pancreas in chronic pancreatitis. A prospective, randomized comparative study after duodenum preserving resection of the head of the pancreas versus Whipple's operation. Chirurg. 1995;66:350-9.

10. Belyaev O, Herzog T, Chromik A, Müller C, Uhl W. Surgery of the pancreas: the surgeon as the crucial prognostic factor (in German with English abstract). Gastroenterologe. 2006;1:34-42.

11. Müller MW, Friess H, Kleeff J, Hinz U, Wente MN, Paramythiotis D, et al. Middle segmental pancreatic resection: an option to treat benign pancreatic body lesions. Ann Surg. 2006;244:909-920.

12. Müller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, et al. Is there still a role for total pancreatectomy? Ann Surg. 2007;246:966-74.

13. Fong ZV, Alvino DM, Castillo CF, Nipp RD, Traeger LN, Ruddy M, et al. Health-related quality of life and functional outcomes in 5-year survivors after pancreaticoduodenectomy. Ann Surg. 2017;266:685-92.

14. Allen CJ, Yakoub D, Macedo FI, Dosch AR, Brosch J, Dudeja V, et al. Long-term quality of life and gastrointestinal functional outcomes after pancreaticoduodenectomy. Ann Surg. 2018;268:657-64.

15. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm. 1974;8:650-5.

16. MP Pai, FP Paloucek. The origin of the "ideal" body weight equations. Ann Pharmacother. 2000;34:1066-9.

17. Frisancho AR (2008) Anthropometric standards. In: An interactive nutritional reference of body size and body composition for children and adults. The University of Michigan Press, United States of America.

18. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2003;26(Suppl 1):S5-S20.

19. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33(Suppl 1):S62-S69.

20. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group. EORTC QLQ-C30. Available at: http://qol.eortc.org/eortc-qlq-c30. Accessed April 28, 2020.

21. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-96.

22. Park JW, Jang JY, Kim EJ, Kang MJ, Kwon W, Chang YR, et al. Effects of pancreatectomy on nutritional state, pancreatic function and quality of life. Br J Surg. 2013;100:1064-70.

23. Heerkens HD, Tseng DSJ, Lips IM, van Santvoort HC, Vriens MR, Hagendoorn J, et al. Health-related quality of life after pancreatic resection for malignancy. Br J Surg. 2016;103:257-66.

24. Heerkens HD, van Berkel L, Tseng DSJ, Monninkhof EM, van Santvoort HC, Hagendoorn J, et al. Long-term health-related quality of life after pancreatic resection for malignancy in patients with and without severe postoperative complications. HPB (Oxford). 2018;20:188-95.

25. Eaton AA, Gonen M, Karanicolas P, Jarnagin WR, D'Angelica MI, DeMatteo R, et al. Health-related quality of life after pancreatectomy: results from a randomized controlled trial. Ann Surg Oncol. 2016;23:2137-45.

26. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN guidelines on enteral nutrition: non-surgical oncology. Clin Nutr. 2006;25:245-59.

27. Geng Y, Qi Q, Sun M, Chen H, Wang P, Chen Z, et al. Prognostic nutritional index predicts survival and correlates with systemic inflammatory response in advanced pancreatic cancer. Eur J Surg Oncol. 2015;41:1508-14.

28. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A, et al. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg. 2011;98:268-74.

29. Su CH, Shyr YM, Lui WY, and P'eng FK. Factors affecting morbidity, mortality and survival after pancreaticoduodenectomy for carcinoma of the ampulla of Vater. Hepatogastroenterology. 1999;46:1973-9.

30. Wu L, Nahm CB, Jamieson NB, Samra J, Clifton-Bligh R, Mittal A, et al. Risk factors for development of diabetes mellitus (Type 3c) after partial pancreatectomy: a systematic review. Clin Endocrinol (Oxf). 2020;92:396-406.

31. Mori Y, Ohtsuka T, Tsutsumi K, Yasui T, Ueda J, Takahata S, et al. Different incretin responses after pancreatoduodenectomy and distal pancreatectomy. Pancreas. 2012;41:455-60.

32. Domínguez-Muñoz JE, Hieronymus C, Sauerbruch T, et al. Fecal elastase test: evaluation of a new noninvasive pancreatic function test. Am J Gastroenterol. 1995;90:1834-37.

33. Vanga RR, Tansel A, Sidiq S, et al. Diagnostic performance of measurement of fecal elastase-1 in detection of exocrine pancreatic insufficiency: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16:1220–28.e4.

34. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep. 2007;9:116-22.

35. Kim H, Yoon YS, Han Y, Kwon W, Kim SW, Han HS, et al. Effects of pancreatic enzyme replacement therapy on body weight and nutritional assessments after pancreatoduodenectomy in a randomized trial. Clin Gastroenterol Hepatol. 2020;18:926-34.

36. Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer. 2001;37:1331-4.

37. Schwarz R, Hinz A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. Eur J Cancer. 2001;37:1345-51.

요약 (국문초록)

서론: 췌장절제술 후 장기 생존자가 증가했음에도 불구하고, 연속적인 환자 및 사전 정의된 경과관찰 프로그램을 통해 전향적으로 개발된 데이터 세트를 기반으로 환자들의 증상, 췌장의 기능 및 삶의 질 등의 연속적인 변화에 대하여 보고한 연구는 매우 드물다. 이 연구는 췌장절제술을 시행 받은 환자들을 대상으로 5년동안 추적 관찰 하면서 그들의 영양상태, 췌장의 기능 및 삶의 질의 변화 양상을 분석하는 것을 목표로 하였다.

방법: 2007 년과 2013 년 사이에 췌십이지장절제술 (PD) 또는 원위췌장절제술 (DP)을 받은 환자들이 연구에 포함되었다. 환자들의 상대 체중 (relative body weight, RBW), 삼두근 피부주름 두께 (triceps skinfold thickness, TSFT), 체질량 지수 (body mass index, BMI), 혈청 단백, 알부민, 트랜스페린 (transferrin), 공복 혈당, 식후혈당, 당화혈색소, 인슐린, C-펩타이드, 대변 엘라스타제 수치 (stool elastase level), 그리고 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30/QLQ-PAN26 설문지 점수들을 5년동안 연속적으로 수집하였다.

결과: 초기에 전체 217명의 환자가 이 연구에 포함되었지만 79명의 환자만이 5년 경과관찰을 완료하였다. RBW, BMI 및 TSFT는 수술 후 계속 감소하였지만 수술 후 6개월부터 증가하기 시작하였다. 트랜스페린, 알부민 및 단백 수치는 수술 후 3개월에 수술 전 수치로 회복되었다. 다변량 분석에서 25 kg/m^{2}를 초과하는 체질량 지수와 보조항암요법이 췌장의 내분비기능장애에 위험인자로 확인되었다. 비록 췌십이지장절제술을 받은 환자들의 지방변과 설사 증상은 수술 후 12개월에 대부분

회복되었지만, 대변 엘라스타제 수치는 수술 후 감소되어 경과 관찰 기간동안 회복되지 않았다. 연구 기간동안 회복되지 않은 설사 척도 점수를 제외하고 대부분의 삶의 질 설문지의 평균 점수들은 수술 후 12개월에 수술 전 수치 이상으로 호전되었다.

결론: 췌장절제술을 시행받은 환자들은 수술 후 12개월에 그들의 일상 생활로 온전히 복귀할 수 있다. 그러나, 췌장 기능 및 삶의 질 관련 위험 인자들이 있는 환자들은 더 주의 깊은 경과 관찰과 지지 요법이 필요하다.

....