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Quality of life after total pancreatectomy with islet autotransplantation for chronic pancreatitis in Japan

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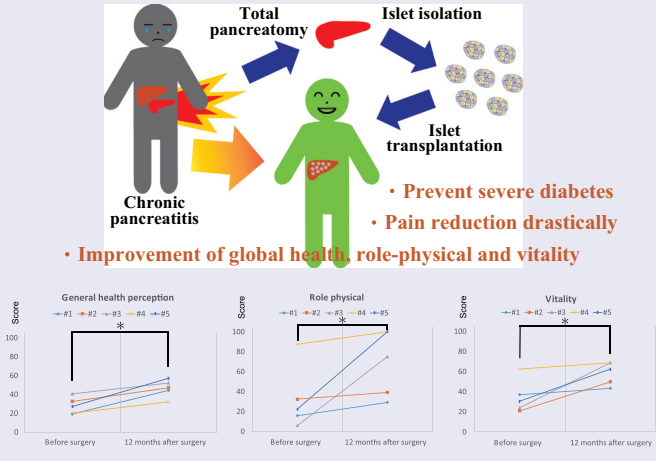
ABSTRACT

Background: Patients with chronic pancreatitis (CP) often have severe and intractable abdominal pain, leading to decreased quality of life (QOL), inability to work or attend school, and increased health care costs due to repeated emergency room visits and hospitalizations.

Methods: We evaluated the efficacy of total pancreatectomy and islet autotransplantation (TPIAT) in terms of pain control and QOL in CP patients treated at our center in Japan. To evaluate QOL, we used the Short-Form 36 Health Survey version 2 (SF-36v2® Standard, Japanese), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and Quality of Life Questionnaire-Pancreatic Modification (QLQ-PAN28).

Results: Between August 2016 and June 2019, we performed this procedure in 5 patients. All patients were followed up for 12 months and all transplanted islets were still functioning at the 1-year follow-up. The major adverse events were abdominal wall hemorrhage, intestinal obstruction, intra-abdominal abscess, and abdominal pain requiring hospitalization; no case had sequelae. No major complications were due to islet transplantation. Pain scores improved postoperatively in all patients. Three QOL item dimensions role-physical ($p = 0.03125$), general health perception ($p = 0.03125$) and vitality ($p = 0.03125$) in the SF-36 were significantly improved 12 months after TPIAT. Mean values of many other QOL items improved, though not significantly.

Conclusion: The QOL improvement after TPIAT for CP suggests its effectiveness in the Japanese population.



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Introduction

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas that eventually culminates in irreversible fibrosis and loss of function.[1] Patients with CP often have severe and intractable abdominal pain that leads to decreased quality of life (QOL), inability to work or attend school, and increased health care costs due to repeated emergency room visits and hospitalizations.[2,3] The first-line treatment for CP includes a low-fat diet, pancreatic enzyme therapy to reduce pancreatic irritation, comprehensive pain management, and endoscopic sphincterotomy and stenting by endoscopic retrograde cholangiopancreatography (ERCP).[4,5] If medical or ERCP therapy is unsuccessful, surgical treatment, such as pancreatic duct drainage or parenchymal resection, may be considered, depending on the morphology of the pancreatic duct and tissue. Total pancreatectomy (TP) with islet autotransplantation (TPIAT) may also be considered in some patients, particularly those with diffuse small pancreatic duct disease, hereditary pancreatitis, or a history of failed surgery.[6–8] The aims of TP are to relieve pain and restore QOL, while islet autotransplantation (IAT) is intended to reduce the burden of postoperative diabetes.[9]

According to the Collaborative Islet Transplant Registry (CITR), 827 IATs were performed from 1999 to September 2015 in North America, Europe, and Australia (https://citregistry.org/system/files/1st_AR_Auto.pdf), mostly with total or completion (≥95%) pancreatectomy. However, only a few IAT procedures with pancreatectomy, especially TP have been reported in Asia; there is one report of distal pancreatectomy,[10] and another of pancreatectomy, including 9 recipients who underwent partial pancreatectomy (50%–80%) and 1 who underwent TP.[11] We previously reported 5 Japanese CP patients who underwent TPIAT, identifying endogenous postoperative insulin secretion in all cases,[6] and here we report an additional follow-up concerning QOL before and after TPIAT.

Results

Patient characteristics

Five patients (2 women and 3 men) underwent TPIAT at our hospital during the study period. Their characteristics are summarized in the previous report.[6] Briefly, their median age was 34 (range, 20–52) years and the indication for surgery was intractable abdominal pain in all cases. Two patients had alcohol-induced CP, 2 had hereditary pancreatitis with genetic mutations (one each in *PRSS1* and *SPINK1*), and 1 had idiopathic CP. The median body mass index (calculated as kg/m^2 was 19.8 (range, 17.7–22.4). The median duration of CP was 12 (range, 4–31) years. Two of the 5 patients were preoperatively diagnosed with diabetes.

Isolation of islets

The median islet yield was 270,967 (range, 116,068–467,042) islet equivalents (IEQ) and the median final islet yield was 5618 (range, 2267–13,010) IEQ/g of pancreas.[6] Purification was not performed in 4 of the 5 cases because there was severe atrophy of the exocrine tissue and a small tissue volume (<15 mL). The median viability was 94.8% (range, 89.5%–97.5%). Endotoxin levels were negative (<5 U/kg) in all patients.

Transplantation of islets

The median number of transplanted islets was 4149 (range, 2,038–10,836) IEQ/kg body weight.[6] In all cases, the prepared islets were transplanted through a catheter into the portal vein. The median portal vein pressure before transplantation was 9 (range, 7–13) mmHg and the highest median value after transplantation was 10 (range, 8–15) mmHg, indicating no significant increase in portal vein pressure. All patients had transient elevations in liver enzymes that resolved spontaneously. There were no serious adverse events associated with islet transplantation.

Evaluation of pain

The primary endpoint was the percentage of patients with improved pancreatic pain (a > 50% reduction in the Izbicki pain score[12] from the preoperative value) and good glycemic control without severe hypoglycemic episodes during the 12

months (365 ± 14 days) after surgery. Please refer to the Patients and Methods section for details. The primary endpoint was achieved in 4 patients. The success rate was estimated to be 80% (80% confidence interval: 0.35–1.00, $p = 0.0026$). Because the lower limit of the confidence interval exceeded the threshold of 20%, significance was reached for efficacy. Four patients (80%) did not require narcotic analgesics at 12 months postoperatively. The remaining patient (#1) did not meet the pain criteria for the primary endpoint. But all patients' Izbicki pain scores improved significantly 12 months postoperative from preoperative using Wilcoxon one-tailed signed rank test ($p = 0.03125$) (Table 1). Moreover, there was an improvement in the visual analog scale (VAS) pain score for all patients, including this patient (#1) significantly analyzed by Wilcoxon one-tailed signed rank test ($p = 0.03125$) (Table 1).

Evaluation of QOL based on the SF-36v2

Although the physical, mental, and social aspects of the component summary scores based on the Short-Form-36 Health Survey version 2 (SF-36v2) did not show any significant changes, the average of each of the 3 component summary scores improved 1 year after TPIAT (Figure 1(a) and Table 2). Among the 8 multi-item dimensions of health, role-physical ($p = 0.03125$), general health perception ($p = 0.0077$) and vitality ($p = 0.035$) improved significantly. As for the other 5 items, role-emotional ($p = 0.070$) was improved or unchanged in all patients, and the other 4 items improved, with the averages scores of physical functioning, bodily pain, social functioning, and mental health increased 12 months after surgery (Figure 1(b) and Table 2).

Evaluation of QOL based on the EORTC QLQ-C30

Although global health status/QOL did not show a significant change, its average considerably improved (Figure 2(a) and Table 3). Moreover, the averages of 4 of the 5 functional scales increased without significant differences, whereas that of the other scale (physical functioning) remained unchanged (Figure 2(b) and Table 3). Among 9 symptom scales, pain ($p = 0.0625$) and financial difficulties ($p = 0.0625$) decreased or was unchanged in all patients without significance (Figure 2(c) and Table 3). The averages of the fatigue, insomnia, appetite loss, constipation, and diarrhea scales decreased, while the other 2 symptom scales – nausea and vomiting as well as dyspnea – generally stayed the same in the 5 patients.

Evaluation of QOL based on the EORTC QLQ-PAN28

Seven of the 18 items – pancreatic pain ($p = 0.023$), bloated abdomen ($p = 0.25$), night pain ($p = 0.25$), flatulence ($p = 0.125$), decreased muscle strength ($p = 0.25$), treatment side effects ($p = 0.25$), fear for future health ($p = 0.125$), and ability to plan ahead ($p = 0.125$)—were improved or unchanged in all patients (Figure 3 and Table 4). Four items improved on average: the average of jaundice, body image, and sexual functioning decreased while satisfaction with health care increased. The averages of indigestion and dry mouth remained unchanged. The other 5 QOL scores worsened compared with before the operation: digestive function scores decreased on average, and the averages of altered bowel functioning, alcohol-related guilt, taste changes, and weight loss increased.

Glycemic control

One of the primary endpoints is good glycemic control defined as HbA1c < 7.4% or less than the preoperative value plus 1.0% in patients with preoperative diabetes without severe hypoglycemic

Table 1. Izbicki pain scores and visual analog scale pain scores before and 12 months after the operation.

Items	Mean (Before surgery)	Medians and IQRs (Before surgery)	Mean (12 months after surgery)	Medians and IQRs (12 months after surgery)	p-value	Significance
Izbicki pain score	79.6	83 (66–90)	18	0 (0–3)	0.03125	*
Visual analog scale pain score	9	9 (8–10)	0.3	0.3 (0–2.86)	0.03125	*

Note: *, $p < 0.05$. IQR, Interquartile Range.

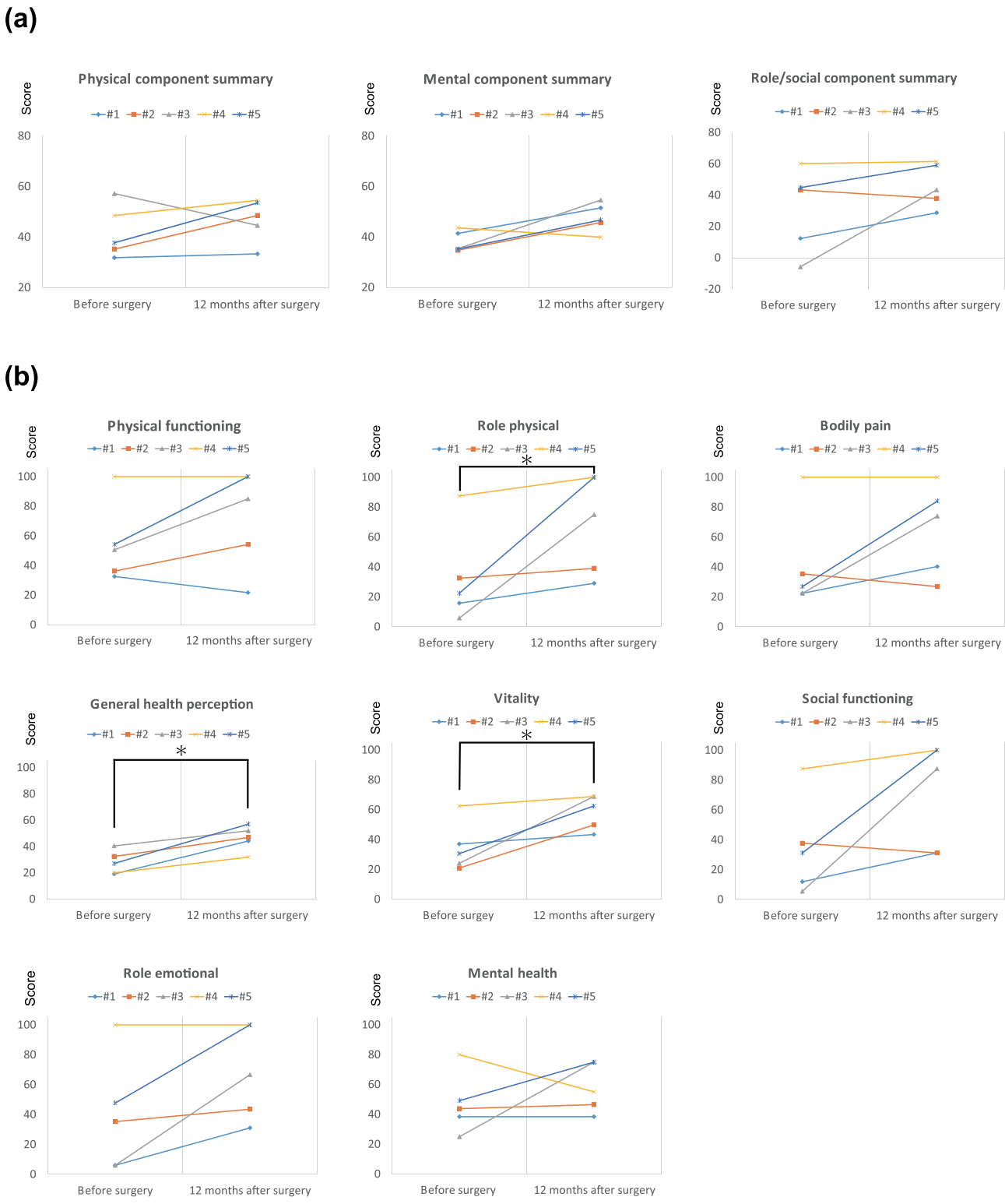

Figure 1. Comparison of quality of life (QOL) between before and 12 months after the operation, using the short-form 36 health survey version 2 (SF-36v2 Standard, Japanese). (a) the physical, mental, and social aspects of the component summary scores. (b) the 8 multi-item dimensions of health. *, $p < 0.05$.

episodes during the 12 months after surgery. No severe hypoglycemic episode was observed. One of the 5 patients had diabetes (A1c 7.1%) before surgery without insulin treatment and maintained A1c less than 8.1% (preoperative value plus 1.0%) after surgery with insulin therapy (Table 5). After surgery, the 3 of the other 4 patients needed exogenous insulin administration, but kept A1c 7.0% or less.

Table 2. Comparison of quality of life (QOL) between before and 12 months after the operation, using the short-form 36 health survey version 2 (SF-36v2 Standard, Japanese).

Items	Mean (Before surgery)	Medians and IQRs (Before surgery)	Mean (12 months after surgery)	Medians and IQRs (12 months after surgery)	p-value	Significance
Physical component summary	42.08	37.7 (35.2–48.5)	46.88	48.5 (44.6–53.5)	0.15625	
Mental component summary	38.04	35.3 (35.2–41.4)	47.68	46.7 (45.7–51.5)	0.0625	
Role/social component summary	30.94	43.3 (12.3–44.8)	46.06	43.3 (37.9–59)	0.09375	
Physical functioning	54.72	50.6 (36.2–54.2)	72.18	85 (54.2–100)	0.125	
Role physical	32.84	22.5 (15.8–32.5)	68.64	75 (39.1–100)	0.03125	*
Bodily pain	41.42	26.9 (22.4–35.4)	65.04	74 (40.3–84)	0.125	
General health perception	27.84	27.1 (20–32.5)	46.42	46.9 (44.2–52)	0.03125	*
Vitality	35.02	30.6 (24.1–37)	58.66	62.5 (49.8–68.8)	0.03125	*
Social functioning	34.76	31.2 (11.9–37.7)	69.98	87.5 (31.2–100)	0.0625	
Role emotional	39.04	35.3 (6.1–47.7)	68.28	66.7 (43.6–100)	0.0625	
Mental health	47.26	43.8 (38.4–49.1)	57.98	55 (46.5–75)	0.1875	

Note: *, $p < 0.05$. IQR, Interquartile Range.

One patient remained insulin-free with A1c less than 6.5% after surgery.

Discussion

Our findings indicate that significant pain relief was achieved in all 5 patients (Table 1) and that 4 patients no longer needed narcotic analgesics at 12 months after surgery (80%), which is equivalent to the results of previous reports.[9,13] The HbA1c value was<7.4% at 12 months postoperatively in all patients (Table 5). Four of the 5 patients required insulin therapy but had C-peptide present in blood without severe hypoglycemia.[6] Since IAT prevented severe hypoglycemia and stabilized blood glucose levels, it is thought that a decline in QOL was not so prominent in spite of daily insulin treatment and that QOL increase associated with the pain relief exceeded the QOL decrease derived from insulin injection. If we compare a TPIAT group with an only TP group as a control group, the effect of IAT on QOL becomes clear, however, due to the established efficacy of IAT, the no-IAT group cannot be performed for ethical reasons. Although it is unable to evaluate the effect of IAT alone on QOL, we evaluated the impact of TPIAT as a whole in this study. Thus, our results revealed that TPIAT performed in our hospital is also effective in CP patients with severe pain that persists despite medical, endoscopic, and other surgical treatments.

On the other hand, most QOL scores improved but not significantly so. One reason for this may be the small sample size. However, given the findings of significant improvements in role-physical, general health perception and vitality of the SF-36 (Figure 1 and Table 2), even with the small sample size, TPIAT should be further evaluated for CP patients.

In most of the items other than those mentioned above, the average value improved. In the SF-36, all of the averages of the 3 component summary scores and 8 multi-item scales increased or improved (Figure 1 and Table 2). It is worth noting that improvements were obtained in not only physical QOL, but also psycho-emotional and social QOL.

In the EORTC QLQ-C30, global health status and 4 of the 5 functional scales increased on average, and the other item, physical functioning, remained unchanged. Moreover, all symptom scales also improved or remained flat on average. Specifically, the averages of nausea and vomiting, as well as dyspnea, were unchanged, but the others were decreased (i.e., improved). In particular, financial difficulties was improved in all patients (the score was originally 0 in 1 patient, so it could not be improved further) ($p = 0.0625$), which suggests that TPIAT is helpful for employment and/or reducing medical expenses (Figure 2 and Table 3).

Most of the items in the QLQ-PAN28 had good results, but some items were a little complicated (Figure 3 and Table 4). Items that remained unchanged or decreased, that is, improved, in all 5 patients were physical symptoms such as pancreatic pain, night pain, bloated abdomen, flatulence, decreased muscle strength, and treatment side effects, as well as mental

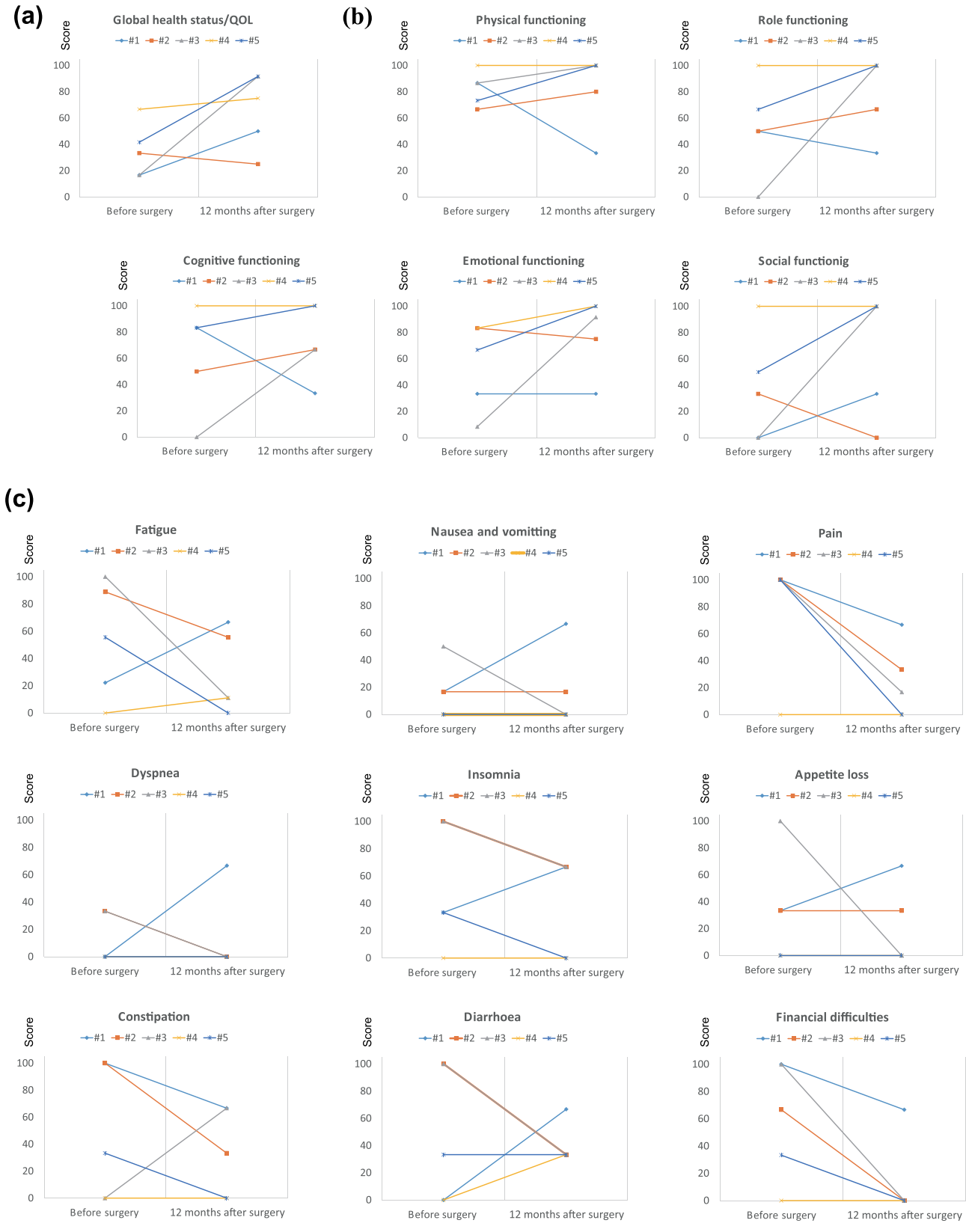

Figure 2. Comparison of quality of life (QOL) between before and 12 months after the operation using the European organization for research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30). (a) Global health status/QOL. (b) Functional scales. (c) Symptom scales.

Table 3. Comparison of quality of life (QOL) between before and 12 months after the operation using the European organization for research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30).

Items	Mean (Before surgery)	Medians and IQRs (Before surgery)	Mean (12 months after surgery)	Medians and IQRs (12 months after surgery)	p-value	Significance
Global health status/QOL	35.002	33.33 (16.67–41.67)	66.668	75 (50–91.67)	0.09375	
Physical functioning	82.668	86.67 (73.33–86.67)	82.666	100 (80–100)	0.375	
Role functioning	53.334	50 (50–66.67)	80	100 (66.67–100)	0.1875	
Cognitive functioning	63.332	83.33 (50–83.33)	73.334	66.67 (66.67–100)	0.3125	
Emotional functioning	54.998	66.67 (33.33–83.33)	80	91.67 (75–100)	0.125	
Social functioning	36.666	33.33 (0–50)	66.666	100 (33.33–100)	0.1875	
Fatigue	53.334	55.56 (22.22–88.89)	28.89	11.11 (11.11–55.56)	0.21875	
Nausea and vomitting	16.668	16.67 (0–16.67)	16.668	0 (0–16.67)	0.75	
Pain	80	100 (100–100)	23.334	16.67 (0–33.33)	0.0625	
Dyspnea	13.332	0 (0–33.33)	13.334	0 (0–0)	0.625	
Insomnia	53.332	33.33 (33.33–100)	40.002	66.67 (0–66.67)	0.5	
Appetite loss	33.332	33.33 (0–33.33)	20	0 (0–33.33)	0.5	
Constipation	46.666	33.33 (0–100)	33.334	33.33 (0–66.67)	0.375	
Diarrhea	46.666	33.33 (0–100)	39.998	33.33 (33.33–33.33)	0.5	
Financial difficulties	60	66.67 (33.33–100)	13.334	0 (0–0)	0.0625	

Note: *, $p < 0.05$. IQR, Interquartile Range.

symptoms such as fear for future health and ability to plan ahead. It should be noted that the outlook for the future improved. On average, in the 5 patients, 4 items improved other than the above 8 items. Specifically, scores for satisfaction with health care increased while those for jaundice, body image, and sexual functioning decreased (i.e., improved). The improvement in body image and sexual functioning is an interesting result because it seems, at first glance, to be unrelated to TPIAT.

Some items appear to have worsened. For example, the decrease in digestive function may be due to TP. The increase in altered bowel functioning may reflect frequent stools, which may also be due to decreased digestive function, but may also be due to increased appetite after TP. Alcohol-related guilt increased, but this is not necessarily a bad result because it seems natural to feel guilty about drinking after TPIAT. Feeling guilty suggests that a patient may be drinking, but that the amount of drinking is suppressed. Because a change in taste refers to a change from the previous taste, the increased score of taste changes may indicate a change for the better. Weight loss reflects pessimistic feelings about low weight. It may have negative psychological consequences but may also lead to a positive willingness to gain weight.

It is well-known that IAT plays a significant role in preventing brittle diabetes after TP.[14] Although postoperative insulin injection is often required after TPIAT, the result that QOL such as role-physical and vitality in patients even who required insulin after TPIAT improved significantly from before operation is interesting, but consistent with a previous report.[7] This suggests that the impact on QOL change after TPIAT exceeds that on compulsory insulin injections. From another points of view, because early surgery results in more effective pain relief and better preservation of pancreatic exocrine and endocrine function[15] and insulin independence occurs in one quarter of adults and half the children after TPIAT,[7] it is expected that transplantation at a younger age is more likely to lower pain and achieve insulin-free. We recommend that TPIAT be considered as soon as possible in patients with poor pain control after endoscopic drainage or partial resection of the pancreas and in those with diffuse CP and hereditary pancreatitis.

In summary, although TPIAT often results in diminished digestive function and onset or worsening diabetes with daily insulin treatment, it improves physical and mental QOLs, and even social behaviors.

The present work has some limitations. First, our study has a small sample size. Second, there could be multiple interpretations of the questionnaire, depending on the patient. Finally, questionnaires are a subjective evaluation. In spite of the limited number of sample size, the result of SF-36 questionnaire which was consistent with the previous paper[7] confirmed the validity of this questionnaire. Compared to SF-36 which is usually used for QOL after

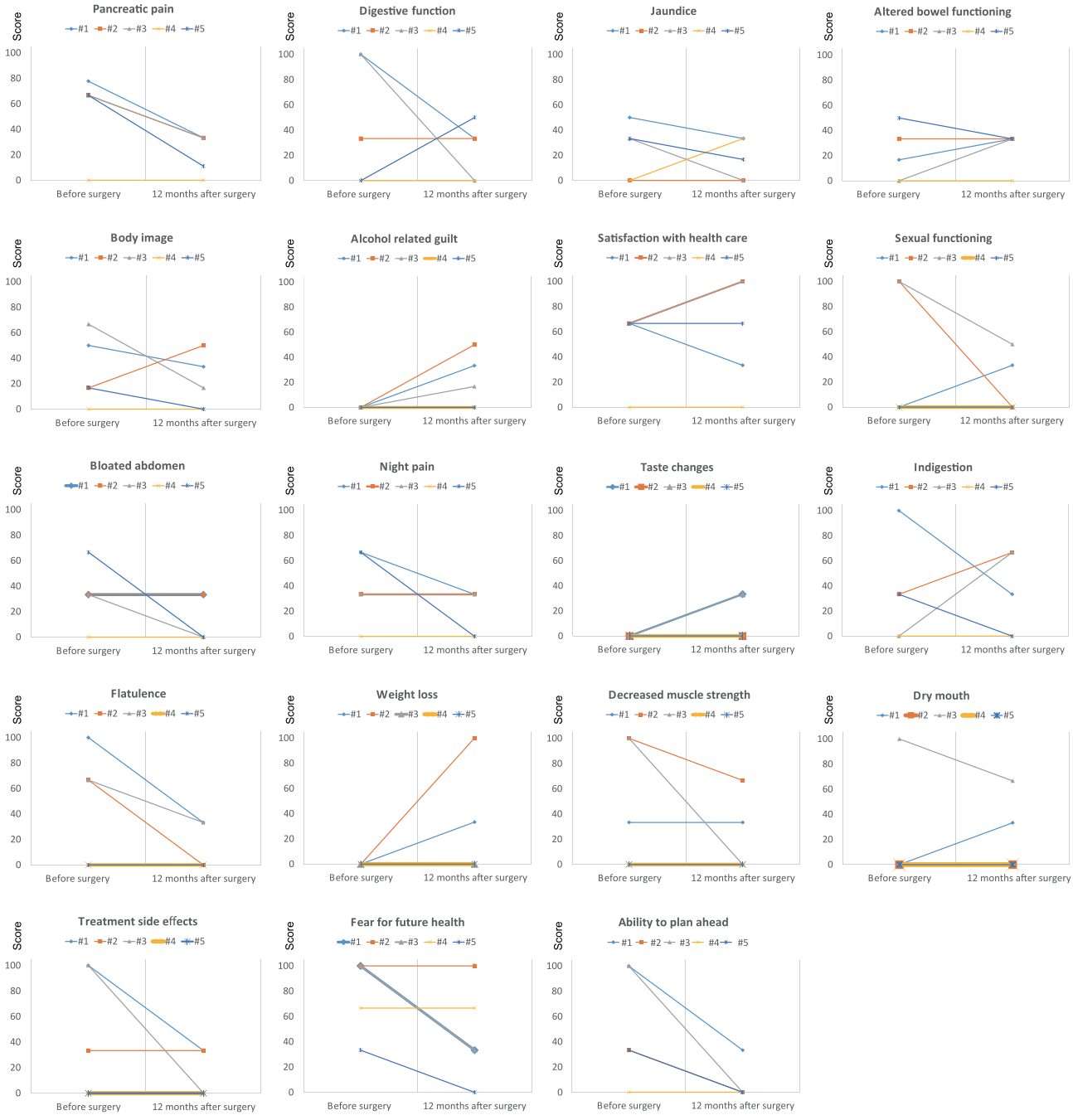

Figure 3. Comparison of quality of life (QOL) between before and 12 months after the operation using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire pancreatic modification (EORTC QLQ-PAN28).

TPIAT,[7,9,16–19] EORTC QLQ-C30, which is a cancer-specific questionnaire developed in 1980 by European Organization for Research and Treatment of Cancer (EORTC),[20] and QLQ-PAN28, a validated version for CP,[21,22] have not been used to assess QOL after TPIAT. Another noteworthy questionnaire is a pancreatitis quality of life instrument (PANQOLI) which is the first CP-specific instrument with a unique subscale for "self-worth"[23,24] and has been used for evaluating QOL of CP patients including Japan.[25–27] The validity of these questionnaires for QOL evaluation in TPIAT needs further verification.

This is a rare report on QOL after TPIAT performed in Asia, and its findings suggest that this

Table 4. Comparison of quality of life (QOL) between before and 12 months after the operation using the European organization for research and treatment of cancer quality of life questionnaire pancreatic modification (EORTC QLQ-PAN28).

Items	Mean (Before surgery)	Medians and IQRs (Before surgery)	Mean (12 months after surgery)	Medians and IQRs (12 months after surgery)	p-value	Significance
Pancreatic pain	55.558	66.67 (66.67–66.67)	22.22	33.33 (11.11–33.33)	0.0625	
Digestive function	46.666	33.33 (0–100)	23.332	33.33 (0–33.33)	0.875	
Jaundice	23.332	33.33 (0–33.33)	16.666	16.67 (0–33.33)	0.375	
Altered bowel functioning	20	16.67 (0–33.33)	26.664	33.33 (33.33–33.33)	0.375	
Body image	30.002	16.67 (16.67–50)	20	16.67 (0–33.33)	0.3125	
Alcohol related guilt	0	0 (0–0)	20	16.67 (0–33.33)	0.125	
Satisfaction with health care	53.336	66.67 (66.67–66.67)	60	66.67 (33.33–100)	0.625	
sexual	40	0 (0–100)	16.666	0 (0–33.33)	0.25	
Bloated abdomen	33.332	33.33 (33.33–33.33)	13.332	0 (0–33.33)	0.25	
Night pain	40	33.33 (33.33–66.67)	19.998	33.33 (0–33.33)	0.25	
Taste changes	0	0 (0–0)	13.332	0 (0–33.33)	0.25	
Indigestion	33.332	33.33 (0–33.33)	33.334	33.33 (0–66.67)	0.625	
Flatulence	46.668	66.67 (0–66.67)	13.332	0 (0–33.33)	0.125	
Weight loss	0	0 (0–0)	26.666	0 (0–33.33)	0.25	
Decreased muscle strength	46.666	33.33 (0–100)	20	0 (0–33.33)	0.25	
Dry mouth	20	0 (0–0)	20	0 (0–33.33)	0.75	
Treatment side effects	46.666	33.33 (0–100)	13.332	0 (0–33.33)	0.25	
Fear for future health	80	100 (66.67–100)	46.666	33.33 (33.33–66.67)	0.125	
Ability to plan ahead	53.332	33.33 (33.33–100)	6.666	0 (0–0)	0.125	

Note: *, $p < 0.05$. IQR, Interquartile Range.

Table 5. Transition of HbA1c(%) (Daily insulin dose (units)).

Patient number	Before surgery	3 months after surgery	6 months after surgery	9 months after surgery	12 months after surgery
#1	7.1 (-)	7.4 (25)	7.8 (15)	7.9 (38)	6.7 (28)
#2	5.7 (-)	7.0 (27)	6.6 (12)	6.5 (10)	7.0 (7)
#3	5.8 (-)	6.2 (19)	5.8 (20)	6.3 (21)	6.8 (21)
#4	5.4 (-)	6.2 (10)	6.3 (13)	6.8 (19)	6.3 (25)
#5	5.6 (-)	6.2 (-)	6.4 (-)	6.3 (-)	6.0 (-)
Median	5.7	6.2	6.4	6.5	6.7
Interquartile Range	5.6–5.8	6.2–7	6.3–6.6	6.3–6.8	6.3–6.8
p-value	-	0.03125	0.0625	0.03125	0.0625

Note: Daily insulin doses are shown in parentheses (units/day) along with HbA1c.
A p -value is based on Wilcoxon one-tailed signed rank test compared with before surgery.

procedure would be useful in East Asia, as in the United States. We plan to conduct a multicenter clinical trial that includes a larger number of patients to evaluate the efficacy of this treatment in more detail.

Patients and methods

Study design

This study was conducted based on the clinical trial "Clinical Study of Pancreatectomy with Autologous Islet Transplantation for Treatment of Chronic Pancreatitis" (UMIN000014368). The protocol for this study was approved by our institutional ethical review board (NCGM-G-001325) and the Committee for Specific Designated Regenerative Medicine (PC3160124). Patients who underwent TPIAT between August 2016 and June 2019 and had 12 months of postoperative follow-up were enrolled in this study. Written informed consent was obtained from all participants.

Selection of patients for TPIAT

Patients with CP and pain refractory to medical and endoscopic treatment were eligible for TPIAT. Narcotic analgesics were used for pain relief in all cases. Patients were ineligible for the procedure if they were alcohol-dependent or did not have sufficient support to manage the complex regimen needed after TPIAT.

Endpoints

The primary endpoint was the percentage of patients with improved pancreatic pain (a > 50% reduction in the Izbicki pain score[12] from the preoperative value) and good glycemic control without severe hypoglycemic episodes during the 12 months (365 ± 14 days) after surgery. Good glycemic control was defined as an HbA1c value<7.4% (National Glycohemoglobin Standardization Program) or less than the preoperative value plus 1.0% in patients with preoperative diabetes and no severe hypoglycemic events from 30 days to 12 months after surgery. Secondary endpoints included assessment of pain, glycemic control, and QOL. Pain scores were averaged over the previous 7 days.

Total pancreatectomy

All patients underwent TP, which was performed using the standard technique. The pancreas was often atrophic, fibrotic, hard, and adherent to the surrounding tissue. The splenic artery and/or gastroduodenal artery were preserved until just before pancreatic resection to minimize the warm ischemia time. The spleen was resected in all cases. The pancreas was transported by the two-layer method[28] after intraductal organ preservation[29] and delivered to the cell processing facility for islet isolation. The gastrointestinal tract was reconstructed by simultaneous gastrojejunostomy and choledochojejunostomy. If necessary, a jejunal tube was placed for postoperative nutritional support. The patient then remained in the operating room with an open abdomen until islet transplantation.

Isolation of pancreatic islets

A digestive enzyme solution (Liberase MTF C/T GMP Grade, Roche Diagnostics) was injected into the main pancreatic duct through a previously placed angiocatheter. If necessary, additional enzyme solution was manually injected into the poorly distended portion of the pancreas using a needle and syringe. The pancreas was then cut into multiple pieces, transferred to a Ricordi® chamber, and manually shaken to promote mechanical and enzymatic digestion. If the volume of tissue after digestion exceeded 15 mL, it was purified by density gradient centrifugation. The pancreatic tissue density was measured before purification.[30] The islets were purified using the bottle method and a mixture of OptiPrep® solution (Axis Shield) and ETK solution (Otsuka Pharmaceutical Factory).[31] The purified islets were then washed and counted under a microscope. The islet yield was expressed as IEQ. The islets were also tested for viability (using a fluorescent dye inclusion/exclusion assay), endotoxin levels (limulus amebocyte lysate assay, <5 EU/kg), and sterility (by Gram staining). The final samples were subjected to bacterial and fungal culture.

Transplantation of islets

After isolation of the islets, a 5-Fr angiocatheter was inserted into the inferior mesenteric vein under direct vision and the tip was placed in the main portal vein. The isolated islets were suspended in 200 mL of a solution containing 10% human albumin and heparin (70 U per kg body weight) and infused into the portal vein. The portal vein pressure was monitored at the beginning, middle, and end of the islet infusion. Intravenous or subcutaneous heparin was continued for 1 week postoperatively to prevent thromboembolism. Doppler ultrasonography of the portal vein was performed within 24 h after transplantation to confirm portal blood flow. The blood glucose level was maintained at 80–110 mg/dL by an artificial pancreas intraoperatively and for several hours postoperatively to protect the transplanted islets.[32]

Follow-up

The patients were observed in the hospital for 4–6 weeks postoperatively or longer if necessary. Thereafter, they attended outpatient clinics on a regular basis. All patients took a sufficient dose of digestive enzyme medication with each meal (pancrelipase 1800 mg/day). Insulin doses were set by a diabetologist according to glycemic control.

Pain and QOL evaluation

Pain scores were evaluated using a VAS and the Izbicki pain score[33] preoperatively and 12 months postoperatively. QOL was quantified based on 3 questionnaires. The first was the SF-36v2® [34] (SF-36v2® Standard, Japanese[35,36], which was created in conjunction with the Medical Outcome Study (MOS), a medical evaluation study conducted in the United States in the 1980s and used in previous reports on TPIAT for CP.[7,9,16] It comprises 36 questions that measure 8 domain scores (role-physical, role-emotional, physical functioning, social functioning, mental health, vitality, bodily pain, and general health perception) and 3 summary scores (physical, mental, and role/social component summaries) aggregated from the 8 scales above. The other questionnaires were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[20,37] and its pancreatic modification (QLQ-PAN28), modified from the QLQ-PAN26 pancreatic cancer module,[21,22] both of which have been used to determine QOL scores in CP.[22,38–40] REDCap® electronic data capture tools were used to collect and manage study data.[41]

Statistical analysis

Pain scores and QOL scores before and 12 months after surgery were compared using Wilcoxon signed rank test, one-tailed. All statistical analyses were performed using OriginPro2016 (OriginLab Corporation) and SAS version 9.4 (SAS Institute Inc.). A p-value<0.05 was considered statistically significant.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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