의학석사 학위논문

Comparison of Long-term Clinical Outcome between External and Internal Pancreatic Stent in Pancreatoduodenectomy

췌십이지장절제술 후 췌관 삽입 방법에 따른 후기 합병증 발생 및 췌장 기능 변화에 관한 무작위 전향적 연구

2016년 8월

서울대학교 대학원

의학과 외과학

신용찬

Abstract

Comparison of Long-term Clinical Outcome between External and Internal Pancreatic Stent in Pancreatoduodenectomy

Yong Chan Shin

Department of Medicine

The Graduate School

Seoul National University

Purpose: In our previous prospective randomized trial, external stent group showed higher rate of clinically relevant postoperative pancreatic fistula (POPF) compared with internal stent group in performing pancreaticojejunal anastomosis after pancreatoduodenectomy (PD). Thus, the purpose of this study was to determine the most appropriate pancreatic drainage method by investigating differences in long-term clinical outcome related with stent between external and internal pancreatic stent groups after postoperative 12 months.

Methods: From August 2010 to January 2014, total 213 patients who underwent PD with duct to mucosa pancreaticojejunostomy were enrolled in this prospective randomized controlled trial (NCT01023594). Among them, 185 patients (97 external and 88 internal stent groups) have been taken follow-up and evaluated via outpatient clinic for 12 months. Their long-term clinical outcomes were compared, including late complications, volume status of remnant pancreas, pancreatic function, and quality of life.

Results: Overall late complication rate for postoperative 12 months was 15.5 % (n=15) in external stent group and 18.2 % (n=16) in internal stent group (P=0.621). In the external group, there were 5 cases of complications associated with removal of stent including peritonitis after

removal and acute abdominal pain resulted from unintended extraction. The internal stent was migrated from pancreaticojejunal anastomosis site within 3 months in 57 patients (64.8%). Even though there were 24 cases of abnormal migration of internal stent including pancreatic duct, intrahepatic duct, and hepaticojejunal anastomosis site, however, there were no associated complications identified for 12 months. Pancreatic duct diameter at postoperative 12 months was comparable between 2 groups (3.24±1.40mm vs. 3.30±1.46mm, *P*=0.806). There was no significant difference in comparison of patients with pancreatic ductal stricture or dilatation divided according to migration time of internal stent. The rate of patients with atrophy of the remnant pancreatic volume of more than 50 % after postoperative 12 months was 39.2 % in external group and 43.2 % in internal group (*P*=0.580). As factors associated with pancreatic exocrine or endocrine function, stool elastase level (63.6±88.3 vs. 73.7±109.9, *P*=0.571) and rate of patients with new-onset diabetes at postoperative 12 months (24.3% vs. 12.5%, *P* = 0.179) were also comparable. There were no significant differences in quality of life evaluated by EORTC QLQ-C30 and QLQ PAN26 between 2 groups at postoperative 12 months.

Conclusion: External and internal stent showed comparable clinical outcomes in long-term follow-up as well as short-term results. The type of pancreatic stent can be selected by the operator according to their preference.

…….

Keywords: pancreaticoduodenectomy, stent, comparison, randomized
Student Number: 2014-25036

Contents

List of Tables

List of Figures

Introduction

Pancreaticoduodenectomy (PD) is performed for a variety of benign or malignant conditions of the periampullary region. Despite the marked reduction in mortality rates to < 5% in many institutions around the world, postoperative pancreatic fistula (POPF) still occurs in 5% to 40% after PD and may cause intra-abdominal abscess, pseudoaneurysmal bleeding, and postoperative mortality by autolytic activity of pancreatic juice.[1-3]

How to best prevent POPF after PD is the most challenging issue that lacks consensus. There have been many attempts to reduce the incidence of POPF by numerous modalities, such as technical variation of reconstruction, somatostatin analogues, pancreatic stenting, and pancreatic drainage.[4] Although many surgeons have used two types of pancreatic ductal stent, external or internal for pancreaticojejunal anastomosis, the outcomes of external and internal stenting trials are often discordant,[5-9] and definitive evidence regarding the optimal surgical technique to reduce POPF rates is still lacking.

Therefore, previously, multicenter, parallel group, prospective randomized trial was performed to determine the most appropriate pancreatic stenting method by investigating differences in early outcomes between external and internal stenting after PD.[10] 328 patients enrolled from 4 tertiary referral hospitals were randomized to external (n=164) or internal (n=164) stent groups and underwent elective PD or pylorus-preserving PD (PPPD) with duct-to-mucosa pancreaticojejunostomy. The external stent group showed higher rate (24.4%) of clinically relevant postoperative pancreatic fistula (POPF) compared with internal stent group (18.9%; risk difference, 5.5%; 90% confidence interval, 2.0% to 13.0%). Although the degree of complications was mild, stent-related complications, including stent obstruction, transient peritonitis, and pancreatitis, occurred in the external stent group. Therefore, this previous trial demonstrated that internal stents seem to be superior to external stents in terms of early clinical outcome and convenient postoperative drain management. This short-term follow-up study has

been ongoing with respect to secondary endpoints, including pancreatic function, remnant pancreatic volume, long-term complications, and quality of life 1 years after PD.

Thus, in view of the importance of long-term follow-up data, we here report on 1 year follow-up data of this trial to make a final decision for the most appropriate pancreatic drainage method.

Material and methods

Patients and Study Design

From August 2010 to January 2014, total 213 patients who underwent elective PD or PPPD with duct-to-mucosa pancreaticojejunostomy at Seoul National University Hospital, among patients enrolled in the previous randomized, controlled, parallel-group, equivalence trial (NCT01023594) conducted to test the hypothesis that the rates of POPF after PD is similar with external and internal stenting, were enrolled in this prospective randomized controlled trial for analysis of long-term clinical outcome. The study complied with the Declaration of Helsinki and was approved and overseen by the institutional review board.

Inclusion and Exclusion Criteria

In our previous study, patients were included if they (1) were 20 to 85 years of age; (2) had no history of previous chemotherapy, radiotherapy, or abdominal surgery; (3) had no severe comorbidities such as liver cirrhosis or end stage renal disease; and (4) provided written informed consent. Patients found to have too small (< 1 mm) or too large (> 5 mm) pancreatic ducts were excluded.

In this study, patients were included if they have been taken follow-up and evaluated via outpatient clinic without a history of other abdominal surgery for 12 months after surgery at Seoul National University Hospital.

Surgical Procedures and Perioperative Management

PD or PPPD was performed according to the individual surgeon. Pancreaticojejunostomy was performed in an end-to-side, duct-to-mucosal, two-layer manner. A 4-10 Fr silastic polyethylene tube was inserted externally or internally into the pancreatic duct as a stent according to random allocation. In the internal stent group, 3 cm of the distal side of the stent was placed in the

jejunum. In the external stent group, the catheter exited via a small enterotomy 10~15 cm below the anastomosis, and was externalized through a stab incision in the anterior abdominal wall. Fibrin glue was applied during every pancreaticojejunostomy. One to three Jackson-Pratt drains were routinely placed anterior and posterior to the pancreaticojejunostomy.

Both the aspect and volume of drains were recorded daily. The serum and drain fluid amylase levels were measured on postoperative days 1, 3, 5, 7, and 10. A contrast computed tomography scan was performed on day 5-7 to detect any complications including POPF, to establish the intra-abdominal extent of the fistula, and to decide on the best management strategy. The peripancreatic drains were then removed if there was no evidence of leakage. Early clinical outcomes of both groups were evaluated and analysed during 6 weeks after the operation at which the external stent was removed in outpatient clinic, including the rate of clinically relevant POPF occurrence, overall complications, and risk factors for clinically relevant POPF.

Study Endpoints

The primary endpoint of this study was long-term complications, including stent-related complications and pancreatic duct size change. The secondary endpoint was the evaluation of the pancreatic function, remnant pancreatic volume, and quality of life at 1 year after the operation.

Endocrine Function Evaluation

Endocrine function was evaluated by measuring concentrations of fasting blood glucose (FBG), blood glucose 2 h after an oral glucose tolerance test (OGTT) with 75 g glucose (PP2), serum c-peptide, serum HbA1c, and serum insulin. Glycemic control was classified as normal, impaired fasting glucose (IFG), and diabetes mellitus (DM), based on American Diabetes Association guidelines.[11] IFG was defined as FBG > 100 mg/dL or PP2 of 140-200 mg/dL and DM was defined as FBG > 126 mg/dL or PP2 > 200 mg/dL. Endocrine function impairment was defined

as a deterioration of endocrine function control capacity, a change from preoperative normal to postoperative DM. The rate of new-onset DM for 1 year after the operation among patients with preoperative normal glucose was compared between 2 groups.

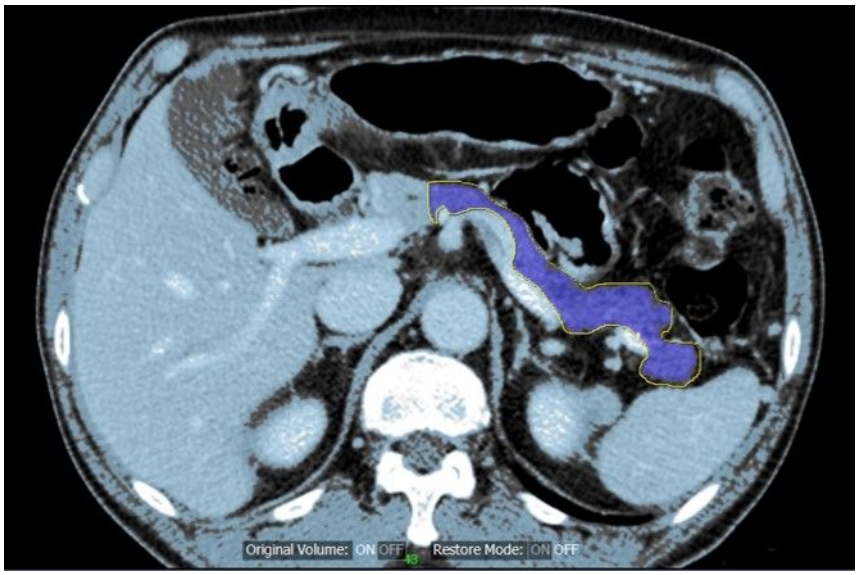
Exocrine Function Evaluation

Exocrine function was evaluated by measuring levels of stool elastase, which is a simple diagnostic test that can be performed on a random stool sample. The stool elastase test is an enzyme-linked immunosorbent assay (ELISA), which uses antibodies against human pancreatic elastase. Human elastase-1 is remarkably stable and is found in the stool in about a six fold concentration as compared with pancreatic juice, thereby stool elastase reflects the secretory capacity of the pancreas.[12] An elastase value < 100 mcg/g of stool is indicative of severe exocrine pancreatic insufficiency (EPI), while levels from 100-200 are described as suggestive of mild EPI. Stool elastase level was measured on Preoperative day, postoperative days 7, and 1 year after the operation.

Pancreas Volumetry

Late-arterial 3-mm-thick three-phase contrast-enhanced axial and coronal computed tomography (CT) scan was performed preoperatively, 1 week postoperatively, and every 3 months from each patient. Pancreas volume was calculated with Xelis 3D software (INFINITT Healthcare, Korea), with vessels and tumors excluded during volume calculation (Fig. 1). The rate of change in remnant pancreatic volume for a year after the operation was calculated as [(postoperative pancreatic volume – one-year pancreatic volume)/postoperative pancreatic volume] x 100 (%).

Figure 1. Pancreas volumetry. Calculated surface area is colored *blue*.



Quality of Life

Quality of life (QoL) was measured between 1 and 2 weeks after operation (immediate postoperation), then at 12 months, using the core cancer QoL assessment module (the EORTC QLQ-C30) and a pancreatic cancer-specific module (the EORTC QLQ-PAN26) developed by the European Organization for Research and Treatment of Cancer (EORTC) QoL study group.[13] Questionnaires were self-reported by patients, but a trained nurse assisted anyone unable to do this. Raw data was converted to a 0 to 100 scale for standardization of the raw scores, as recommended in the EORTC QLQ-C30 scoring manual.

Statistical Analysis

Results are presented as mean ± standard error of the mean. Nominal data were compared using χ^2 test or Fisher's exact test and continuous variables using Student *t* tests and the Mann-Whitney *U* test. The change in remnant pancreatic volume for a year after the operation is presented as a box-and-whisker plot. All statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL), with 2-sided *P* values less than 0.05 considered statistically significant.

Results

Patient Enrollment and Demographic Findings

Between August 2010 and January 2014, a total of 213 patients were enrolled in this long-term study. Of 213 patients, 116 were the external stent group and 97 were the internal stent group. After enrollment, 28 patients were excluded because of (1) death (n = 15), (2) loss of follow-up (n = 10), or (3) a history of other abdominal surgery for 12 months after PD (n = 3). We therefore evaluated a total of 185 patients, 97 in the external stent group and 88 in the internal stent group (Fig. 2).

There were no significant differences in mean age, sex distribution, operative indication, operative method, pancreatic texture, pancreatic stent size, estimated blood loss, and operation time between 2 groups (Table 1). Although the mean postoperative pancreatic duct size in the internal stent group was significantly larger compared to that in the external stent group (P = 0.003), those at postoperative 12 months were comparable (P = 0.806).

Table 2 summarizes the results of the primary outcome. Clinically relevant pancreatic fistula (ISGPF B or C) occurred in 28.9% of patients in the external stent group and 21.6% of patients in the internal stent group (P = 0.256). With regard to complication related to the indwelling or removal of the pancreatic stent, 5 stent-related complications occurred in the external stent group. Two patients experienced transient peritonitis without evidence of pancreatitis immediately after stent removal, which improved without management. Two patients visited the ER after discharge because of external stent obstruction which had no clinical impact. One patient developed pancreatitis after stent removal and was readmitted and conservatively treated. Conservative management including antibiotics or prolonged indwelling (grade II) of a surgical drain were used in 20.6% and 17.0% patients, respectively and radiological intervention (grade IIIa) were required in 19 patients (19.6%) in the external stent group and 12 patients (13.6%) in the internal stent group. No surgical intervention (grade IIIb) was performed for the treatment of

POPF in either group. No life-threatening complication (grade IV) or mortality occurred in either group.

Figure 2. Randomization flowchart

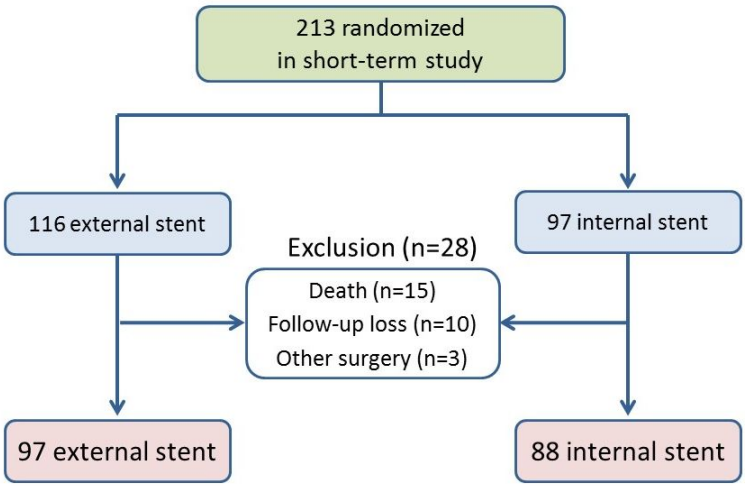


Table 1. Patient demographics*

	External stent (n = 97)	Internal stent (n = 88)	*P*-value
Age (years)†	62 (24, 80)	63 (27, 83)	0.678
Sex (Male)	65 (67.0%)	47 (53.4%)	0.059
BMI (kg/m^2)†	23.6 (17.1, 31.4)	22.95 (14.2, 35.6)	0.029
Preoperative biliary drainage	49 (50.5%)	37 (42.0%)	0.249
Operative indication			0.348
Ampullary, duodenal cancer	26 (26.8%)	26 (29.5%)	
Distal bile duct cancer	30 (30.9%)	19 (21.6%)	
Pancreatic cancer	22 (22.7%)	12 (13.6%)	
Cystic neoplasm	11 (11.3%)	17 (19.3%)	
Neuroendocrine tumor	3 (3.1%)	7 (8.0%)	
Others‡	5 (5.2%)	7 (8.0%)	
Operative method			0.245
PD	22 (22.7%)	14 (15.9%)	
PPPD	75 (77.3%)	74 (84.1%)	
Combined resection	7 (7.2%)	1 (1.1%)	0.067
Vascular resection	5 (5.2%)	1 (1.1%)	0.214
Soft pancreatic texture	67 (69.1%)	69 (78.4%)	0.151
Size of the pancreatic duct (mean, mm)			
Preoperation	3.30±1.56	3.65±2.16	0.210
Postoperation	2.58±0.51	2.89±0.83	0.003
Postoperative 12 months	3.24±1.40	3.30±1.46	0.806
Size of the pancreatic stent (Fr)			0.103
4 - 5	4 (4.1%)	5 (5.7%)	
6 - 7	36 (37.1%)	20 (22.7%)	
8 - 10	57 (58.8%)	63 (71.6%)	
Intraoperative blood loss (mL)	458.2±451.5	364.6±248.1	0.095
Operative time (mean min)	284.6±68.2	272.9±69.5	0.251
Stool elastase level (mcg/ g of stool)			
Preoperation	226.7±163.3	274.7±157.3	0.086
Postoperation	38.3±42.0	62.6±69.9	0.039
Postoperative 12 months	63.6±88.3	73.7±109.9	0.571

*No significant differences were noted according to the type of the stent. †Values are median (95% confidence interval). ‡Metastatic tumor, gastrointestinal stromal tumor, pancreatitis, cholangitis. BMI, body mass index; PD, pancreatoduodectomy; PPPD, pylorus-preserving pancreatoduodenectomy.

Table 2. Postoperative outcomes*

	External stent (n = 97)	Internal stent (n = 88)	*P*-value
Overall complications	63 (64.9%)	50 (56.8%)	0.257
Dindo-Clavien classification			0.505
Grade I / II	11 / 9 (20.6%)	8 / 7 (17.0%)	
Grade IIIa / IIIb	19 / 0 (19.6%)	12 / 0 (13.6%)	
Grade Iva / IVb	0 / 0	0 / 0	
Type of complication			
Wound infection	15 (15.5%)	11 (12.5%)	0.562
Delayed gastric emptying	11 (11.3%)	11 (12.5%)	0.808
Intra-abdominal fluid collection	12 (12.4%)	5 (5.7%)	0.116
Late intra-abdominal bleeding (PPH)	5 (5.2%)	3 (3.4%)	0.560
Bile leak	4 (4.1%)	0	0.123
Stent-related complications†	5 (5.2%)	0	0.061
Early intra-abdominal bleeding	3 (3.1%)	1 (1.1%)	0.623
Chyle leak	1 (1.0%)	3 (3.4%)	0.348
Gastrointestinal bleeding	2 (2.1%)	0	0.498
Pleural effusion	0	1 (1.1%)	0.476
POPF grade B or C	28 (28.9%)	19 (21.6%)	0.256
Duration of drainage (mean days)	15.3±15.6	13.1±9.4	0.266
Length of hospital stay (mean days)	17.4±9.8	16.1±7.9	0.312
ICU utilization	4 (4.1%)	1 (1.1%)	0.371
Mortality	0 (0%)	0 (0%)	1.00

*Postoperative outcomes were evaluated and analyzed during 6 weeks after the operation at which the external stent was removed in outpatient clinic. †Transient peritonitis (2 patients), stent obstruction (2) and pancreatitis (1). PPH, postpancreatectomy hemorrhage; POPF, postoperative pancreatic fistula; ICU, intensive care unit.

Late Complications

The overall rate of late complication during follow-up period since postoperative 6 weeks was comparable between two groups (Table 3).

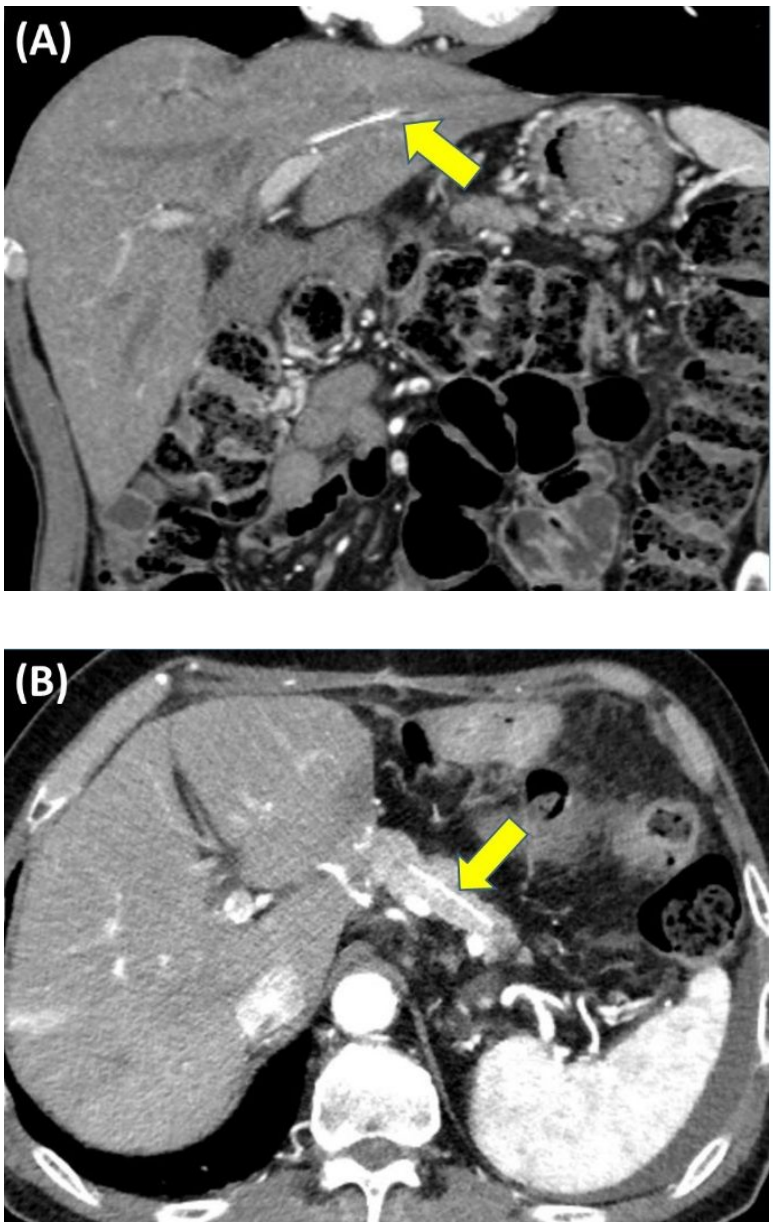
All follow-up CT scans of patients in the internal stent group were reviewed to determine in consensus the stent migration. Of 88 patients, the stent was completely detached from the pancreaticojejunostomy at postoperative 3 months in 57 (64.8%) and 6 months in 22 (25.0%). The stent of 9 patients (10.2%) was not detached during follow-up period. After detachment of the stent, follow-up CT scans showed abnormal stent migration in 9 patients (10.2%), not passing spontaneously into the small intestine and uneventfully through the rectum. The abnormally migrated stents were most commonly located in the hepaticojejunostomy anastomosis (n = 4, 4.5%), followed by the intrahepatic duct (n = 3, 3.4%) and the remnant pancreatic duct (n = 2, 2.3%) (Fig. 3). However, there were no abnormally migrated stent-induced complications identified during follow-up period.

Table 3. Late complications

	External stent (n = 97)	Internal stent (n = 88)	*P*-value
Overall late complications*	15 (15.5%)	16 (18.2%)	0.621
Types of complication			
Wound infection	2 (2.1%)	3 (3.4%)	
Delayed gastric emptying	2 (2.1%)	1 (1.1%)	
Ileus	3 (3.1%)	2 (2.3%)	
Late intra-abdominal bleeding (PPH)	0	1 (1.1%)	
Bile leak	2 (2.1%)	0	
Liver abscess	4 (4.1%)	3 (3.4%)	
Marginal ulcer	0	2 (2.3%)	
Unspecified abdominal pain	2 (2.1%)	4 (4.5%)	
Readmission	12 (12.4%)	13 (14.8%)	0.633

*Overall late complications were evaluated and analyzed during follow-up period since 6 weeks after the operation. PPH, postpancreatectomy hemorrhage.

Figure 3. Abnormal migration of the internal stent in CT image that appears as a high-density linear structure (*yellow arrow*). (A) located in the intrahepatic duct, (B) located in the remnant pancreatic duct

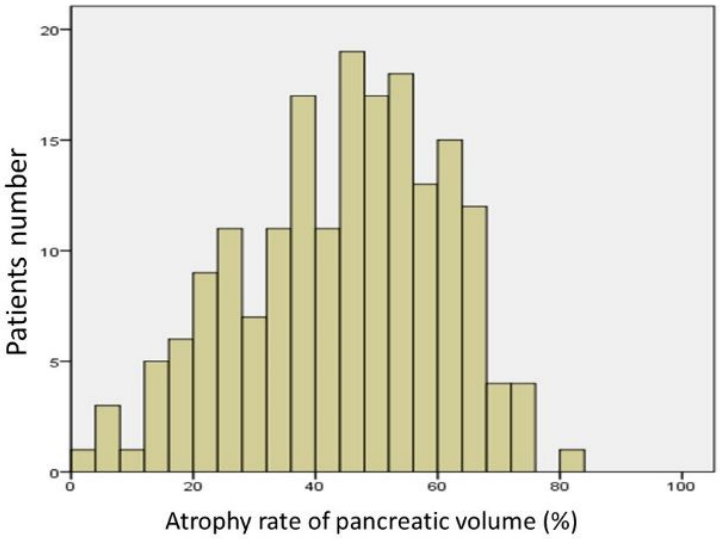


Change in Pancreatic Volume and Duct Size

There was no significant difference in the atrophy rate of remnant pancreas between 2 groups (P = 0.221). The median percentage of change in remnant pancreatic volume for 12 months was 45.2% (range 3.2-82.8 %) in the external stent group and 46.6 (range 6.2-75.1 %) in the internal stent group (Fig. 4).

Although the mean postoperative pancreatic duct size was significantly different between 2 groups (2.58±0.51 vs. 2.89±0.83 mm, P = 0.003), the pancreatic duct size at postoperative 12 months was comparable (3.24±1.40 vs. 3.30±1.46 mm, P = 0.806) (Table 1). The pancreatic ductal dilatation at postoperative 12 months occurred 59.8% in the external stent group and 55.7% in the internal stent group (P = 0.496) (Table 5).

Figure 4. Change in pancreatic volume for postoperative 12 months



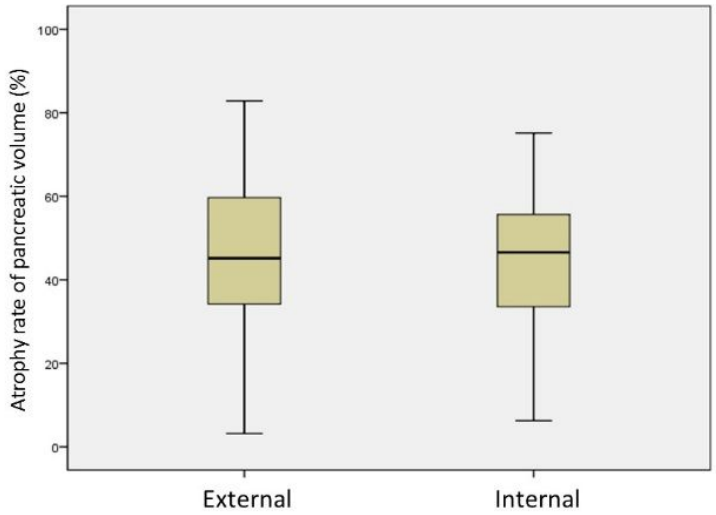


Table 4. Atrophy rate of the remnant pancreas by the detachment time of internal stents

Detachment time	Atrophy rate (%)	*P*-value
3 months	45.5±14.5	0.655
6 months	44.5±14.9	
≥ 6 months	37.4±19.3	
No detachment	46.6±19.4	

Table 5. Duct size change rate of the remnant pancreas in both groups

	External stent (n = 97)	Internal stent (n = 88)	*P*-value
Change rate (R, %)*			0.496
Mild dilatation (0≤R<50)	26 (26.8%)	28 (31.8%)	
Severe dilatation (R≥50)	32 (33.0%)	21 (23.9%)	

*Pancreatic duct size change rate was calculated as [(one-year pancreatic duct size - postoperative pancreatic duct size)/postoperative pancreatic duct size] × 100 (%)

Table 6. Change in pancreatic duct size by the detachment time of internal stents

	Detachment time (months)			
	3 (n=57)	≥ 6 (n=22)	No (n=9)	*P*-value
Dilatation	34 (59.6%)	10 (45.5%)	5 (55.6%)	0.523
Stricture	23 (40.4%)	12 (54.5%)	4 (44.4%)	

Pancreatic Function and Quality of Life

Patients with preoperative normal glucose were 48/97 in the external stent group and 50/88 in the internal stent group. Of the 48 patients in the external stent group, 34 (70.8%) developed endocrine functional impairment, including 27 (56.2%) who developed IFG and 7 (14.6%) who developed overt DM (Fig. 5). Of the 50 patients in the internal stent group, 20 (40.0%) developed IFG and 4 (8.0%) developed DM at postoperative 12 months. There was no significant difference in the rate of new-onset DM for 1 year after the operation between 2 groups ($P = 0.066$).

The stool elastase level of all the patients at postoperative days 7 was lower by a value of severe EPI. Although the stool elastase level was significantly lower in the external stent group than in the internal stent group due to an externalization of the pancreatic juice through the external stent after the operation (38.3±42.0 vs. 62.6±69.9 mcg/g of stool, $P = 0.039$), there was no significant difference in the stool elastase level between 2 groups at 1 year after the operation (Table 1).

Global health status, other functional scales, and pancreatic cancer-specific scales showed similar patterns of change between 2 groups in both immediate postoperation and postoperative 12 months (Table 7, 8, Fig. 6, 7).

Figure 5. Change in pancreatic endocrine function for postoperative 12 months

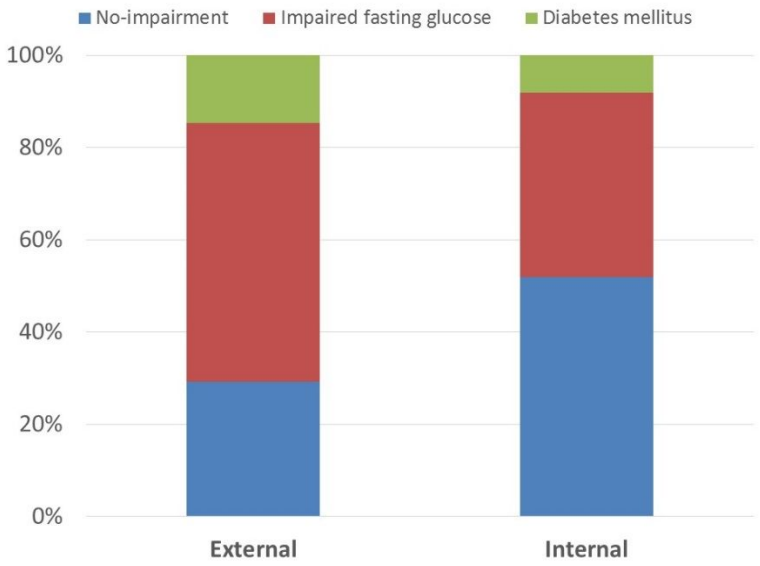


Table 7. Quality of life scores* at immediate postoperation

	External stent (n = 65)	Internal stent (n = 67)	*P*-value
Global health status/QoL†	30.4±20.8	34.5±22.7	0.286
Functional scales†			
Physical	44.7±21.4	47.0±19.9	0.530
Role	33.8±27.8	36.6±28.8	0.582
Emotional	63.3±23.2	64.1±25.7	0.843
Cognitive	66.4±21.1	64.9±20.1	0.675
Social	49.7±30.7	51.0±27.2	0.804
Pancreatic cancer-specific scales ‡			
Pancreatic pain	48.5±27.6	48.0±25.4	0.922
Digestive	57.4±29.0	57.2±27.4	0.964
Hepatic	18.7±28.3	15.4±24.0	0.472
Bowel habit	22.1±25.7	17.7±22.6	0.299
Body image	45.4±29.7	42.3±32.4	0.568
Satisfaction	59.2±25.4	54.0±25.1	0.234
Sexuality†	46.3±37.0	57.8±39.3	0.170

*By EORTC QLQ-C30 and QLQ-PAN26. †A high score for the global health status/QoL, functional scales, and sexuality represents a *high* QoL and *better* function. ‡A high score for the pancreatic cancer-specific scales except for sexuality represents a *worse* QoL. QoL, quality of life.

Table 8. Quality of life scores* at postoperative 12 months.

	External stent (n = 51)	**Internal stent (n = 49)**	*P*-value
Global health status/QoL†	66.3±23.5	67.5±21.6	0.795
Functional scales†			
Physical	78.7±18.0	80.7±13.8	0.537
Role	80.1±22.1	82.3±22.9	0.619
Emotional	84.8±20.3	80.4±16.2	0.239
Cognitive	83.0±18.1	87.2±13.9	0.206
Social	83.3±25.2	82.3±21.1	0.827
Pancreatic cancer-specific scales ‡			
Pancreatic pain	18.5±19.0	15.3±14.9	0.351
Digestive	17.7±21.9	17.7±21.9	1.000
Hepatic	7.8±14.9	9.5±15.2	0.577
Bowel habit	14.0±15.9	15.0±20.5	0.794
Body image	26.1±25.0	26.9±23.8	0.882
Satisfaction	46.0±26.8	41.8±27.0	0.444
Sexuality†	71.7±35.2	65.7±35.5	0.488

*By EORTC QLQ-C30 and QLQ-PAN26. †A high score for the global health status/QoL, functional scales, and sexuality represents a *high* QoL and *better* function. ‡A high score for the pancreatic cancer-specific scales except for sexuality represents a *worse* QoL. QoL, quality of life.

Figure 6. Changes in quality of life using the EORTC QLQ-C30 questionnaire. (A) Immediate postoperation, (B) postoperative 12 months. Each aspect was scored on a scale from 0 to 100.

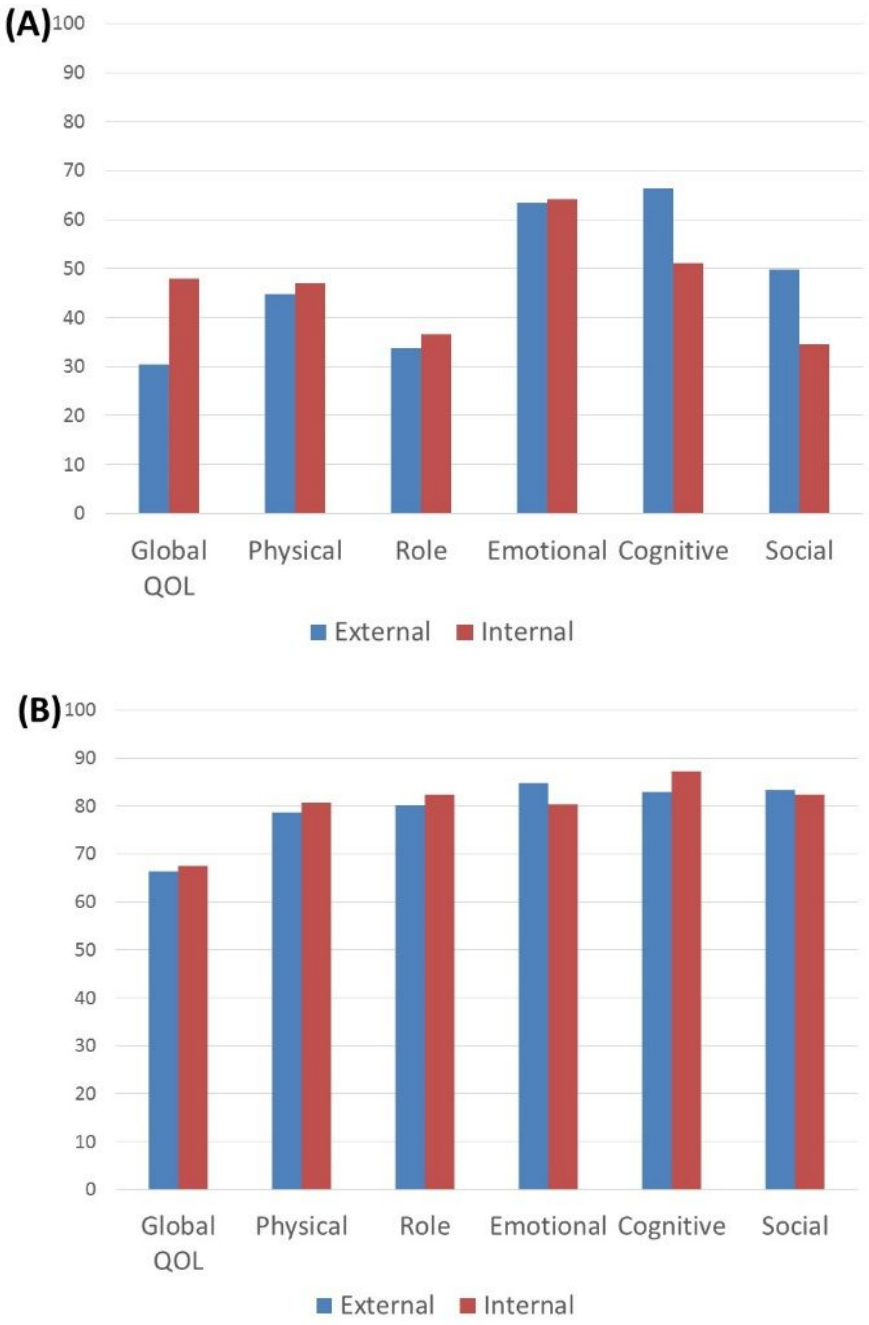
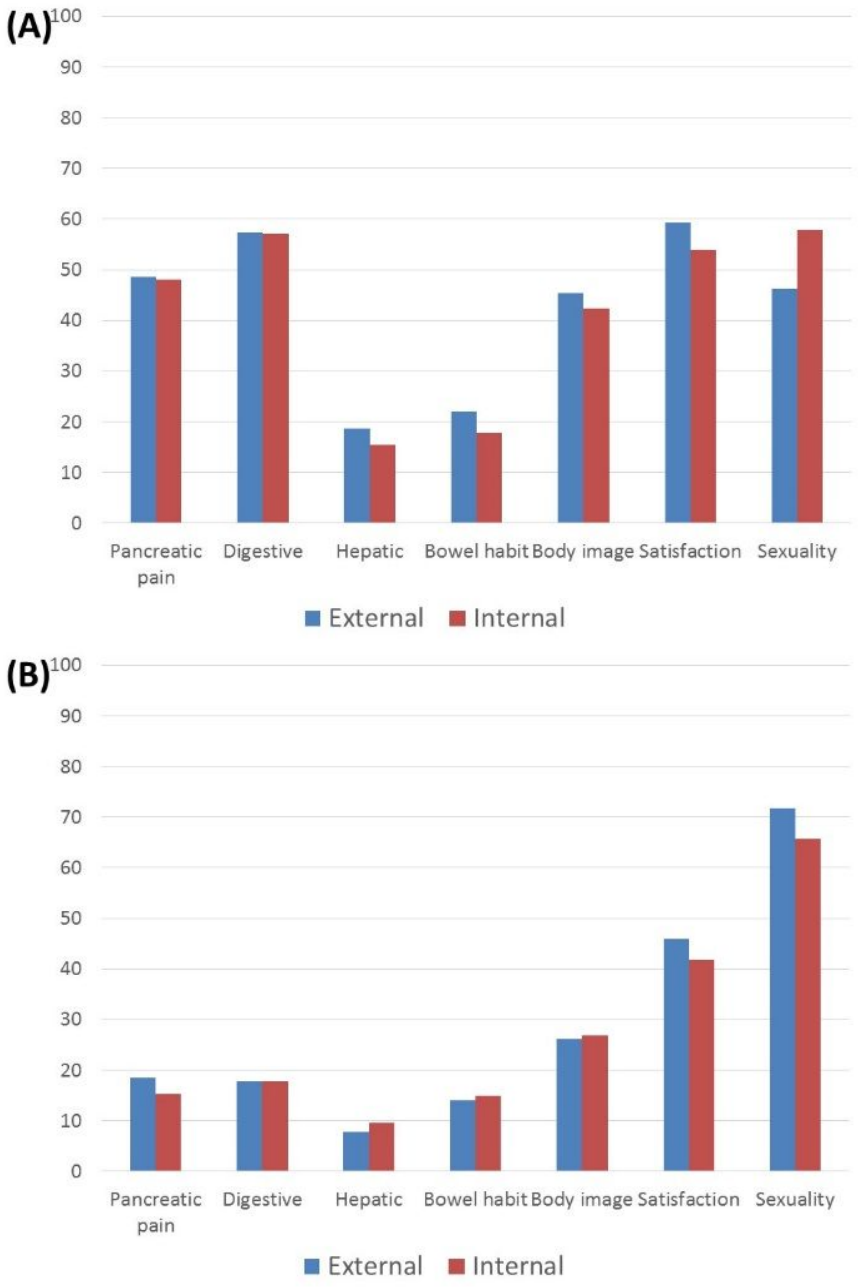


Figure 7. Changes in quality of life using the EORTC QLQ-PAN26 questionnaire. (A) Immediate postoperation, (B) postoperative 12 months. Each aspect was scored on a scale from 0 to 100.



Discussion

Stent placement across the PJ following PD may be useful for the diversion of pancreatic juice from the pancreatic anastomotic site, decompression of the remnant pancreas, and maintaining patency of the main pancreatic duct. However, the benefits remain controversial due to a lack of data. Although several RCTs, observational case series,[3,15,16] and meta-analyses[5,6-8,14] have demonstrated reduced POPF rates with the use of pancreatic stents compared with no stents after PD, previous reports comparing external and internal pancreatic stents are very limited. In previous 2 RCT comparing between external and internal stents, authors reported similar complication rates, including those of POPF.[17,18] The retrospective study, comparing outcomes between external (n = 37) and internal (n = 37) stents, demonstrated the same POPF rate (5.4%) in both group, and therefore recommended the selective use of stents according to individual characteristics such as the presence of ampullary tumors or small pancreatic ducts (< 2 mm).[19] This study is the first report to evaluate long-term clinical outcomes of external and internal stenting as an ongoing study with respect to secondary endpoints of previous short-term trial for determining the most appropriate pancreatic drainage method after PD.

This present RCT was designed to examine the hypothesis that long-term outcomes of external and internal pancreatic stenting could be equal, following an analysis of early outcomes with the POPF rates between 2 groups. In our previous trial, the external stent group showed a higher rate (24.4%) of clinically relevant POPF compared with the internal stent group (18.9%; risk difference, 5.5%; 90% confidence interval, 2.0% to 13.0%). Other postoperative outcomes were comparable between the two groups. In this long-term follow-up study, there were no significant differences in late complications, change in pancreatic volume and duct size, pancreatic endocrine and exocrine function, or quality of life between 2 groups. One of the most common concern about the stent insertion in PD is the stent-induced complication. Five stent-related complications occurred in the external stent group during short-term follow-up period, including transient peritonitis (in 2 patients), stent obstructions (in 2 patients), and pancreatitis (in 1

patient). The removal of external stents is potentially hazardous and obstruction or kinking of the external stent may lead to further complications. The incidence of abnormal stent migration in the internal stent group was 10.2% (9 of 88), including the hepaticojejunostomy anastomosis (4.5%), intrahepatic duct (3.4%), and the remnant pancreatic duct (2.3%). Even though 15 patients (17.0%) with the stent located in jejunal afferent limb was not included in the incidence, the stents may migrate to abnormal areas of the body or penetrate adjacent jejunal wall. Many previous studies reported that the incidence of stent migration into the bile ducts was 7-16.8% after PD with the internal stent.[20,21] In addition, pancreatic and bile duct stents have been reported to cause ductal inflammation and fibrosis, eventually leading to ductal stricture, chronic pancreatitis, and cholangitis. Even though there were no abnormally migrated stent-induced complications identified during follow-up period, it may cause unwanted results. Closed follow-up via out-patient clinic for these patients will be needed.

Another important concern during an analysis of long-term outcomes was about change in pancreatic volume and duct size according to the timing of stent detachment, especially in the internal stent group. In computed tomography (CT) scans performed postoperatively every 3 months from each patient, there was no significant difference in the atrophy rate of the remnant pancreas according to the detachment time of internal stents ($P = 0.655$) (Table 4). In addition, the pancreatic ductal dilatation or stricture rates were comparable between groups divided by the timing of stent detachment ($P = 0.523$) (Table 5, 6).

There were some limitations to our study. First, our previous RCT was multicenter trial, however, this study was limited by a single-center study where all of the operations were performed by 3 hepatobiliary surgeons. It is due to many cases of follow-up loss or no standardization of routine follow-up via outpatient clinic by 4 tertiary referral hospitals, and may cause a selection bias in an analysis of long-term follow-up data. Second, the follow-up duration for evaluation of long-term clinical outcomes after PD was relatively short. More than 2 years after PD may be required for identification of stent-induced complications and

nutritional index.

In conclusion, we discovered comparable long-term outcomes according to external and internal pancreatic stent use after PD. Internal stents may be preferred in terms of early safety and convenient postoperative drain management. Surgeons who selected the internal stent according to their preference have to be concerned about internal stent-induced complications following abnormal migration.

Reference

1. Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. Digestive surgery. 2001;18(6):453-7; discussion 8.

2. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg. 2000;232(6):786-95.

3. Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C, et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg. 2007;246(3):425-33; discussion 33-5.

4. Zhou Y, Zhou Q, Li Z, Lin Q, Gong Y, Chen R. The impact of internal or external transanastomotic pancreatic duct stents following pancreaticojejunostomy. Which one is better? A meta-analysis. J Gastrointest Surg. 2012;16(12):2322-35.

5. Zhou Y, Zhou Q, Li Z, Lin Q, Gong Y, Chen R. The impact of internal or external transanastomotic pancreatic duct stents following pancreaticojejunostomy. Which one is better? A meta-analysis. J Gastrointest Surg. 2012;16(12):2322-35.

6. Hong S, Wang H, Yang S, Yang K. External stent versus no stent for pancreaticojejunostomy: a meta-analysis of randomized controlled trials. J Gastrointest Surg. 2013;17(8):1516-25.

7. Xiong JJ, Altaf K, Mukherjee R, Huang W, Hu WM, Li A, et al. Systematic review and meta-analysis of outcomes after intraoperative pancreatic duct stent placement during pancreaticoduodenectomy. The British journal of surgery. 2012;99(8):1050-61.

8. Zhou Y, Yang C, Wang S, Chen J, Li B. Does external pancreatic duct stent decrease pancreatic fistula rate after pancreatic resection?: a meta-analysis. Pancreatology : official journal of the International Association of Pancreatology. 2011;11(3):362-70.

9. Zhou Y, Zhou Q, Li Z, Chen R. Internal pancreatic duct stent does not decrease pancreatic fistula rate after pancreatic resection: a meta-analysis. Am J Surg. 2013;205(6):718-25.

10. Jang JY, Chang YR, Kim SW, Choi SH, Park SJ, Lee SE, Lim CS, Kang MJ, Lee H, Heo JS, Randomized Multicenter Trial of Comparison of Early Clinical Outcomes

Between Patients Who Underwent External and Internal Pancreatic Stenting During Pancreaticoduodenectomy. Br J Surg. 2016 in submission.

11. Association AD (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33:S62–S69

12. Sziegoleit A, Krause E, Klor HU, et al. Elastase 1 and chymotrypsin B in pancreatic juice and feces. Clin Biochem. 1989;22:85–9.

13. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group. EORTC QLQ-C30. http://groups.eortc.be/qol/eortc-qlq-c30 [accessed 23 March 2013].

14. Wang Q, He XR, Tian JH, Yang KH. Pancreatic duct stents at pancreaticoduodenectomy: a meta-analysis. Digestive surgery. 2013;30(4-6):415-24.

15. Roder JD, Stein HJ, Bottcher KA, Busch R, Heidecke CD, Siewert JR. Stented versus nonstented pancreaticojejunostomy after pancreatoduodenectomy: a prospective study. Ann Surg. 1999;229(1):41-8.

16. Sriussadaporn S, Pak-Art R, Kritayakirana K, Prichayudh S. Pancreaticoduodenectomy with external drainage of the pancreatic remnant. Asian J Surg. 2008;31(4):167-73.

17. Kamoda Y, Fujino Y, Matsumoto I, Shinzeki M, Sakai T, Kuroda Y. Usefulness of performing a pancreaticojejunostomy with an internal stent after a pancreatoduodenectomy. Surg Today. 2008;38(6):524-8.

18. Tani M, Kawai M, Hirono S, Ina S, Miyazawa M, Shimizu A, et al. A prospective randomized controlled trial of internal versus external drainage with pancreaticojejunostomy for pancreaticoduodenectomy. Am J Surg. 2010;199(6):759-64.

19. Ohwada S, Tanahashi Y, Ogawa T, Kawate S, Hamada K, Tago KI, et al. In situ vs ex situ pancreatic duct stents of duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy with billroth I-type reconstruction. Arch Surg. 2002;137(11):1289-93.

20. Kadowaki S, Miura F, Amano H, Toyota N, Wada K, Shibuya M, Maeno S, Takada T, Sano K.Whereabouts ofan internal short stent placed across the pancreaticojejunostomy following pancreatoduodenectomy. J Hepatobiliary Pancreat Sci 2012;19: 566-577.

21. Park SH, Kim JH, Noh SY, Byun JH, Lee SS, Kim HJ, Park SH, Lee SK, Hwang DW,

Kim SC, Han DJ, Lee MG, Migration of Internal Pancreaticojejunostomy Stents into the Bile Ducts in Patients Undergoing Pancreatoduodenectomy. J Gastrointest Surg 2015;19:1995-2002.

요약 (국문초록)

서론: 이전에 시행된 우리의 전향적 무작위 연구에서, 췌십이지장절제술 후 췌문합부위에 스텐트를 삽입하는 방법 중 전췌액 외부배액 시키는 방법을 적용한 환자군(외부배액군)이 짧게 내부배액 시키는 방법을 적용한 환자군 (내부배액군)보다 임상적으로 의미 있는 수술 후 췌장루가 더 높은 비율로 발생하는 것을 보여주었다. 따라서, 이 연구의 목적은 췌십이지장절제술 후 12개월까지 외부배액군 및 내부배액군의 후기 임상 결과를 비교 분석하여 가장 적절한 췌장 배액 방법을 결정하는 것이었다.

방법: 이 전향적 무작위 연구는 2010년 8월부터 2014년 1월까지 췌십이지장절제술을 시행 받은 213명의 환자들 중 12개월동안 외래를 통한 경과 관찰 및 평가를 받은 185명 (외부배액군 97명, 내부배액군 88명)을 대상으로 진행하였다. 두 환자군의 후기 합병증, 잔여췌장실질의 위축 비율, 췌장의 기능 및 삶의 질 등을 비교 분석하였다.

결과: 수술 후 12개월동안 전반적인 후기 합병증은 외부배액군에서 15.5% (n=15), 내부배액군에서 18.2% (n=16) 발생하였다. 외부배액군에서는 스텐트 제거 후에 발생한 일시적인 복막염과 의도치 않은 스텐트 뽑힘에 의해 발생한 복통 등 스텐트 제거와 관련된 5례의 합병증이 발생하였다. 내부배액관은 57명 (64.8%)의 환자에서 3개월 내에 췌장-공장 문합부로부터 떨어져 나왔다. 관찰 기간 동안 떨어진 내부배액관 중 밖으로 배설되지 않고 비정상적으로 잔여췌장실질, 간내담관, 혹은 담도-공장 문합부위에 걸려서 남아있는 경우가 24례 있었으나 그로 인한 합병증은 관찰되지 않았다. 수술 후 12개월에 남아있는 췌장의 주췌관 직경은 두 군 사이에

차이가 없었다 (3.24±1.40mm vs. 3.30±1.46mm, *P*=0.806). 내부배액관의 배출 시기에 따라 분류한 그룹 간의 주췌관 직경의 확장 혹은 협착 비율을 비교하였을 때 유의한 차이는 없었다. 수술 직후에 비해 수술 후 12개월에 50% 이상의 췌장 실질 위축을 보이는 환자 비율은 외부배액군이 39.2%, 내부배액군이 43.2% 였다 (*P*=0.580). 췌장의 외분비 및 내분비 기능 비교를 위해 분석한 인자들로서 수술 후 12개월에 대변 elastase 수치 (63.6±88.3 vs. 73.7±109.9, *P*=0.571)와 새롭게 발생한 당뇨 환자 비율 (24.3% vs. 12.5%, *P* = 0.179)은 두 군 간에 유의한 차이를 보이지 않았다. 또한, EORTC QLQ-C30과 QLQ PAN26을 이용하여 평가한 두 그룹의 삶의 질 평가에서 수술 직후 및 12개월 후 모두 유의한 차이는 없었다.

결론: 외부배액군 및 내부배액군은 조기 합병증뿐만 아니라 후기 임상 결과들과 관련하여 유의한 차이는 없었다. 췌십이지장절제술 시에 삽입하는 스텐트의 종류는 집도의의 주관에 따라 결정할 수 있겠다.

.....

주요어: 췌십이지장절제술, 스텐트, 무작위, 비교

학 번: 2014-25036