

# Effect of Double Layer Polyglycolic Acid Felt for Reducing Pancreatic Fistula After Pancreatoduodenectomy

## Results of a Multicenter Randomized Control Trial (PLANET-PJ trial)

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All the individual participants' data collected during this trial after de-identification and other material (eg, the study protocol, statistical analysis plan, informed consent forms) will be available immediately following publication. All requests should be submitted to the corresponding author for consideration.

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**Objective:** To evaluate the usefulness of a double coating of polyglycolic acid (PGA) felt for pancreaticojejunostomy in reducing the incidence of clinically relevant postoperative pancreatic fistula (POPF) in patients with a normal pancreas.

**Background:** Despite pancreaticojejunostomy being an advanced procedure in patients undergoing pancreatoduodenectomy (PD), few studies have reported a satisfactory reduction in the incidence of POPF.

**Methods:** This study was an international multicenter randomized controlled trial conducted between October 2018 and December 2021. Patients with a main pancreatic duct < 3 mm in diameter and soft pancreas undergoing pancreaticojejunostomy were eligible and randomized to either Arm A (conventional pancreaticojejunostomy) or Arm B (pancreaticojejunostomy using double coating of PGA felt). The primary endpoint was the incidence of grade B/C POPF. This trial was registered at ClinicalTrials.gov (NCT03331718) and Japan Registry of Clinical Trials (jRCTs042180090).

**Results:** A total of 514 patients were enrolled and randomly assigned to the study. The full analysis set population consisted of 508 patients, including 253 patients in Arm A and 255 patients in Arm B. According to the full analysis, the incidence of grade B/C POPF in Arm A was 28%, whereas that in Arm B was 25% (adjusted odds ratio: 0.97, 95% CI: 0.90–1.05;  $P=0.453$ ). The incidence of intra-abdominal abscesses and mortality was also not significantly different between the 2 groups.

**Conclusions:** This study showed that the use of a double coating of PGA felt in patients undergoing pancreaticojejunostomy did not reduce the incidence of grade B/C POPF.

**Key Words:** clinically relevant postoperative pancreatic fistula, pancreatoduodenectomy, polyglycolic acid (PGA) felt, postoperative complications

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Pancreatoduodenectomy (PD) is performed for malignant and benign diseases of the pancreatic head region, including the head of the pancreas, the lower common bile duct, and the ampulla of Vater. The incidence of complications after PD is reported to be 30% to 65%, which is higher than that of other digestive tract surgeries.<sup>1–10</sup> Among these complications, postoperative pancreatic fistula (POPF) is generally recognized as an important complication because subsequent intra-abdominal hemorrhage can be fatal. It also prolongs hospital stay and increases surgical mortality.

Pancreaticojejunostomy generally involves a combination of sutures between the pancreatic parenchyma and the seromuscular layer of the jejunum and duct-to-mucosa sutures. It has been reported that there is a significant association between the risk of clinically relevant POPF and soft pancreatic texture with unexpanded pancreatic ducts.<sup>11,12</sup> A clinical study of various pancreaticojejunostomy techniques was reported to reduce the incidence of POPF. Although there have been some reports of improvements in the incidence of POPF,<sup>8,13</sup> the worldwide consensus is that the incidence of clinically significant POPF remains high, ranging from 10% to 46%.<sup>14–18</sup> Various interventions have been proposed to reduce the incidence of POPF; no definitive technique or medical treatment has yet been identified.<sup>19,20</sup> In other words, to date, few studies have reported a satisfactory reduction in the incidence of pancreatic jejunal anastomosis.

Polyglycolic acid (PGA) felt is a felt-like absorbable suture-reinforcing material that is used to reinforce fragile tissues such as the lung, liver, and vessels.<sup>21–23</sup> Here, we devised a new method using double coating of PGA felt for pancreaticojejunostomy in patients with a small diameter of the main pancreatic duct (MPD). We conducted an international multicenter randomized phase III (PLANET-PJ) trial in Japan and the Republic of Korea to verify the usefulness of double coating of PGA felt for preventing POPF.

## METHODS

### Study Design

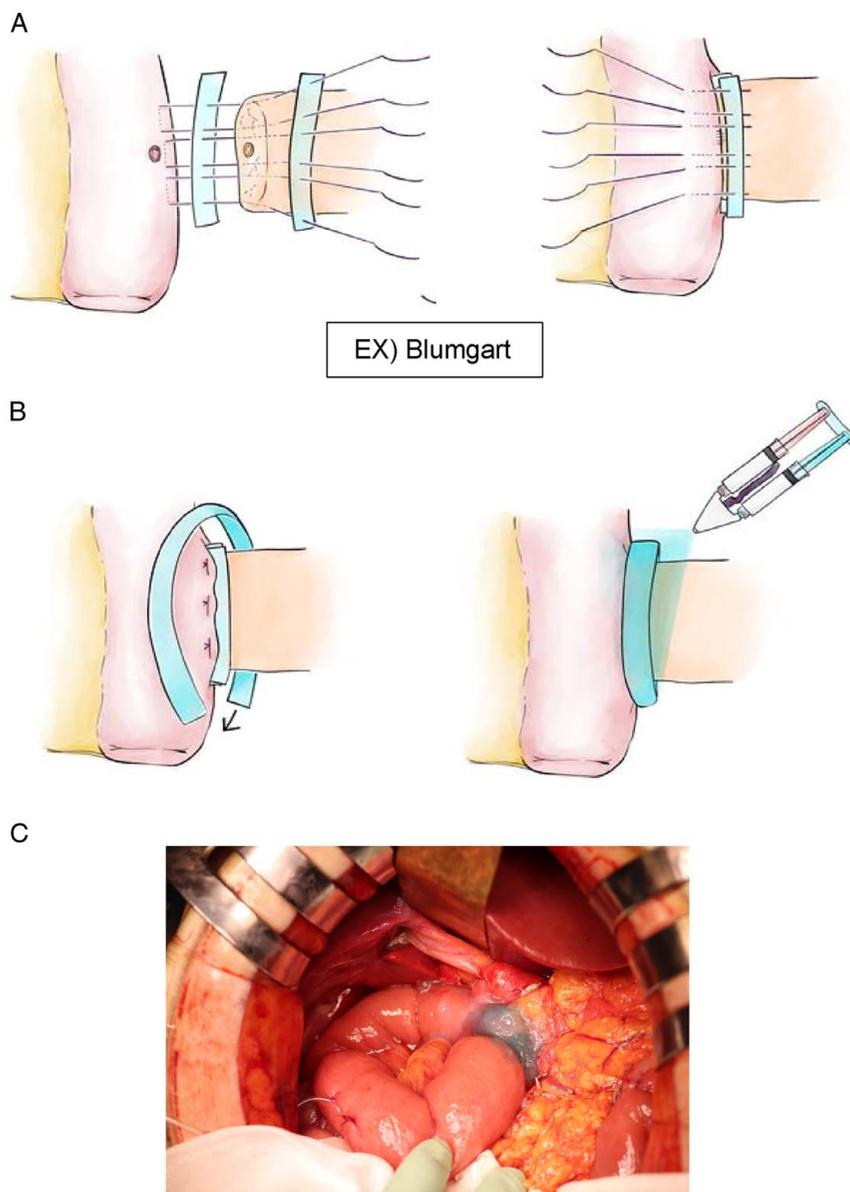
This trial (PLANET-PJ) was designed as a multicenter randomized phase III trial and included 32 institutions in Japan and the Republic of Korea (Supplemental Data File 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>). This study aimed to evaluate the efficacy of the PGA felt reinforcement technique in preventing POPF after pancreaticojejunostomy compared with that of the conventional technique in patients with an MPD < 3 mm in diameter and a soft pancreas who underwent PD. We hypothesized that compared with conventional anastomosis, the new pancreaticojejunostomy method using double coating of PGA felt would reduce the incidence of grade B/C POPF. All the investigators involved in this study were conducted in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013), the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labour, and Welfare of Japan, and the ethical guidelines for medical and health research involving human subjects in Japan. Written informed consent was obtained from all the enrolled patients. Ethical approval for this study was obtained from the Clinical Research Review Board of the University of Toyama and the study protocol was published internationally (Supplemental Data File 2, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>).<sup>24</sup>

### Patients

Patients without a dilated MPD (so-called soft pancreas) and without parenchymal atrophy or pancreatitis who were scheduled to undergo pancreaticojejunostomy were eligible for inclusion in this study. There were no restrictions on disease type. Preoperative imaging was used to determine whether the MPD diameter of each patient was < 3 mm. The MPD diameter was measured before pancreaticojejunostomy to confirm that it was 3 mm or less intraoperatively. A detailed overview of eligibility criteria is presented in Supplemental Data File 3, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>.

### Randomization and Interventions

After confirming eligibility and obtaining written informed consent, patients were randomized at a 1:1 allocation ratio to either Arm A (conventional pancreaticojejunostomy) or Arm B (pancreaticojejunostomy with a double coating of PGA felt for reinforcement) preoperatively. Central randomization and registration were performed using an electronic data capture (EDC) system (Seoul National University, Medical Research Collaborating Center). Patients were stratified by institution and suturing method (mattress or nonmattress). We used Pocock and Simon's minimization method for random assignment and Mersenne Twister for random number generation. All



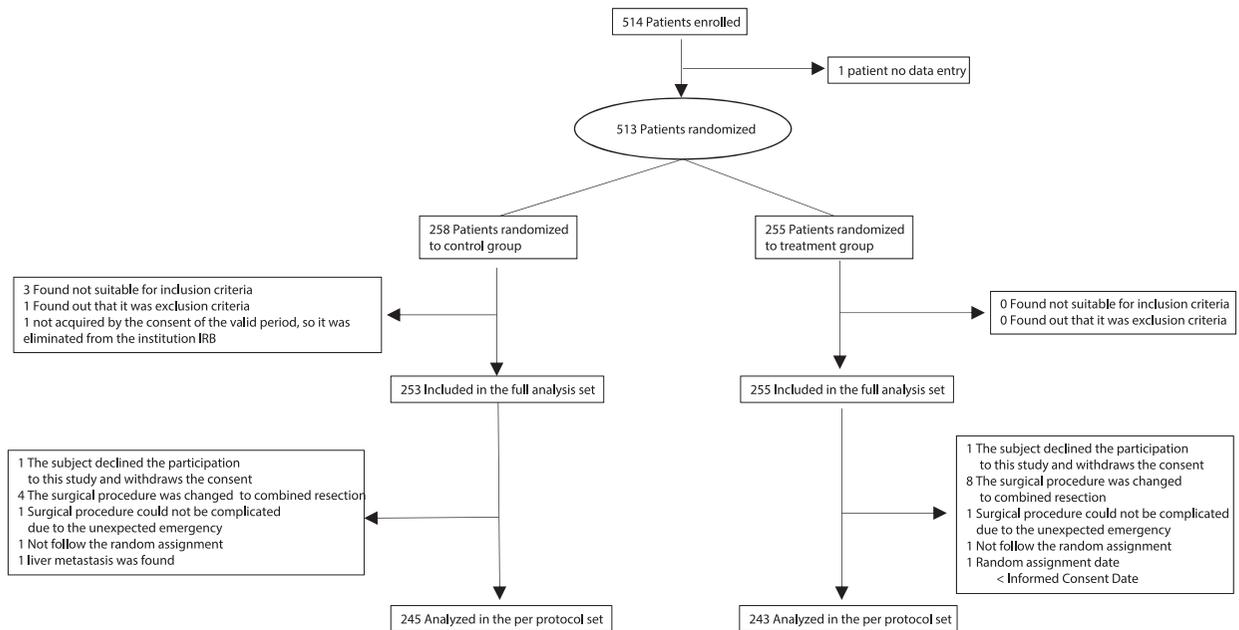
**FIGURE 1.** (A) First layer PGA felt in Arm B. (B) Second layer PGA felt in Arm B. (C) Intraoperative photograph at the time of the placement of the 0.15-mm polyglycolic acid felt.

enrolled patients were blinded to the surgical procedure they were to undergo by randomization. Blinding of the surgeons was not possible due to the different techniques used during pancreaticojejunostomy, but the outcome was assessed by an independent researcher who was blinded to the surgical procedures.

Patients scheduled to undergo pancreaticojejunostomy with duct-to-mucosa anastomosis were eligible for inclusion; however, there were no restrictions on the suturing method used to suture the pancreas and the jejunum (Kakita method, 2-layer suturing method, modified Blumgart method, etc.). However, patients who were scheduled to undergo pancreaticogastrostomy and for whom the invagination method would be used were not eligible.

MPD diameter was measured intraoperatively immediately before pancreaticojejunostomy to confirm that it was 3 mm or less. There were no restrictions on the placement of the pancreatic stent (yes/no) or the method (external/internal).

The study continued even if the suturing method used to suture the pancreas and the jejunum changed during surgery (mattress or nonmattress sutures). Anastomotic drains were used in all the patients. There were no restrictions on the type or number of anastomotic drains. However, a closed-type drain had to be used and placed around the pancreaticojejunostomy site. In Arm A, pancreaticojejunostomy was performed, as described above. In Arm B, during pancreaticojejunostomy, (1) PGA felt with a thickness of 0.3 mm (Neoveil, GUNZE MEDICAL, Japan) was placed on both the ventral and dorsal sides of the pancreatic parenchyma. A suture was then placed between the pancreatic parenchyma and the jejunum (Fig. 1A and Supplemental Data File 4, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>). (2) Before abdominal closure (after all reconstructions and after washing the abdominal cavity), PGA felt with a thickness of 0.15 mm was applied to the site of the anastomosis, and fibrin glue was sprayed (Figs. 1B, C).



**FIGURE 2.** Study flowchart for this study: Japan-Korea Multicenter Prospective Randomized Control Trial (PLANET-PJ Trial).

To confirm that the anastomotic procedures were conducted as allocated at the time of central randomization, photographs were taken of all patients. A central judgment was conducted for all included patients. At that time, the photographs were reviewed by 2 members of the committee.

At each participating institution, 2 to 4 expert pancreatic surgeons performed the operations. To minimize technical variability, standardized surgical protocols and instructional videos were provided to all participating institutions before patient enrollment. Surgeons were required to adhere to these protocols throughout the study, with particular emphasis placed on ensuring that the handling and application of PGA felt were performed in a standardized manner.

A 3-month follow-up after surgery was conducted to determine the occurrence of postoperative complications, rehospitalization, and reoperation, and was included in the treatment protocol. Three months after surgery, contrast-enhanced CT (or MRI) was performed to measure MPD diameter in both arms.

### Assessments

The primary endpoint was the incidence of grade B/C POPF. The secondary endpoints were outcome measures related to surgery, such as operative duration, blood loss volume, duration of drain placement after surgery, length of hospital stay after surgery, incidence of overall biochemical leak and POPF, incidence of delayed gastric emptying (DGE), incidence of intra-abdominal abscesses, incidence of postpancreatectomy hemorrhage (PPH), incidence of interventional drainage, incidence of overall postoperative complications, incidence of POPF-related complications (POPF+DGE+abscess+PPH), incidence of mortality, and incidence of reoperation.

Biochemical leak, POPF,<sup>25</sup> DGE,<sup>26</sup> and PPH<sup>27</sup> were defined and graded according to the International Study Group of Pancreatic Surgery (ISGPS) criteria and the

Clavien–Dindo classification.<sup>28</sup> Postoperative complications other than POPF, DGE, and PPH were graded according to the Clavien–Dindo classification.<sup>28</sup>

### Statistical Analysis

This study was designed to evaluate the efficacy of Arm B compared with Arm A in terms of the incidence of POPF. In patients for whom PGA felt was used at the pancreaticojejunostomy site during PD with an MPD diameter of 3 mm or less, the incidence of POPF was 15.5%.<sup>29,30</sup> In a previous study in which PGA felt was not used at the pancreaticojejunostomy site in PD patients with an MPD diameter of 3 mm or less, the incidence of POPF was 26%.<sup>31</sup> When the difference in POPF incidence was greater than or equal to 10.5%, the difference was considered statistically significant at a significance level of  $\alpha = 0.05$  (2-sided). The minimum number of patients required to obtain a power of 100 (1- $\beta$ ) of at least 80% using the Fisher exact test was 231 patients per group. Furthermore, as ~10% of the patients were expected to be ineligible for surgery, the sample size was ultimately increased to 514 patients (257 patients per arm).

The Fisher exact test was used to evaluate the primary endpoints. The adjusted odds ratios and 95% CIs for the incidence of grade B/C POPF between Arm A and Arm B were calculated using multiple logistic regression analysis; the suturing method to suture the pancreas and the jejunum (mattress or nonmattress sutures) was included as a covariate. The incidence rates of grade B/C POPF for each arm were summarized as frequencies and incidence proportions with Clopper–Pearson's exact 95% CIs.

For the secondary endpoints, we compared categorical variables using the Fisher exact test and continuous variables using the Wilcoxon test. For comparison of the secondary efficacy endpoints, 2-sided statistical tests with a significance level of 0.05 were used because the results for the secondary endpoints should be interpreted as explanatory. In addition, the incidence of adverse events was

**TABLE 1.** Preoperative Patients' Baseline Clinical Characteristics in the Full Analysis Set

Characteristics	Arm A (control) (n = 253)		Arm B (polyglycolic acid felt reinforcement) (n = 255)	
	N (%)	Missing value	N (%)	Missing value
Patients' background characteristics				
Age (yr)	71 (26–89)	0	70 (25–91)	0
Sex		0		0
Male	157 (62.1)		157 (61.6)	
Female	96 (37.9)		98 (38.4)	
Body mass index (kg/m <sup>2</sup> )	23.8 (16.0–41.1)	0	23.7 (15.8–38.3)	0
Performance status		0		0
0	215 (85)		225 (88.2)	
1	38 (15)		30 (11.8)	
Diabetes mellitus		0		0
No	191 (75.4)		182 (71.4)	
Yes	62 (34.6)		73 (28.6)	
Steroid use		0		0
No	252 (99.6)		254 (99.6)	
Yes	31 (0.4)		1 (0.4)	
Anticoagulant use		0		0
No	214 (84.6)		213 (83.5)	
Yes	39 (15.4)		42 (16.5)	
Cardiovascular disease		0		0
No	240 (94.9)		247 (96.9)	
Yes	13 (5.1)		8 (3.1)	
Main pancreatic duct diameter (mm)	2.0 (0.0–3.0)	0	2.0 (0.5–3.0)	0
Pancreatic thickness (mm)	14.6 (4.5–30.2)	23	13.3 (5.0–30.0)	20
Pancreatic atrophy		0		0
No	249 (94.9)		247 (96.9)	
Yes	13 (5.1)		8 (3.1)	
Preoperative biliary drainage		0		0
No	103 (40.7)		114 (44.7)	
Yes	150 (59.3)		141 (55.3)	
ERBD	124	9	115	7
Plastic	104		100	
Metallic	11		8	
ENBD*	18		14	
PTBD*	19		23	
Primary disease		0		0
Pancreatic cancer	18 (7.1)		27 (10.6)	
Intraductal papillary mucinous neoplasm	18 (7.1)		18 (7.1)	
Pancreatic neuroendocrine neoplasm	13 (5.1)		19 (7.5)	
Distal bile duct cancer	125 (49.4)		114 (44.7)	
Ampulla of Vater cancer	47 (18.6)		45 (17.6)	
Others	32 (12.7)		32 (12.5)	
Preoperative laboratory data				
White blood cell count (cells/mm <sup>3</sup> )	5860 (2680–13220)	0	5830 (2600–11360)	0
Hemoglobin (g/dL)	12.5 (9.0–16.6)	0	12.7 (9.3–17.7)	0
Platelet count (×10 <sup>4</sup> /mm <sup>3</sup> )	23.9 (10.3–58.6)	0	23.4 (11.6–55.3)	0
Total bilirubin (mg/dL)	0.8 (0.20–13.3)	0	0.8 (0.20–10.9)	0
Creatinine (mg/dL)	0.7 (0.4–1.7)	0	0.7 (0.3–1.8)	0
Albumin (g/dL)	3.9 (2.4–5.1)	0	4.0 (2.7–5.0)	0
Serum amylase (IU/L)	71 (15–509)	8	74 (22–746)	70
Hemoglobin A1c (%)	5.8 (4.1–10.8)	38	5.8 (4.3–10.2)	32
Modulator for allocation				
Procedure of pancreaticojejunostomy		5		6
Mattress	204 (82.3)		210 (84.3)	
Nonmattress	44 (17.7)		39 (15.7)	

Data are expressed as the median (range) for continuous variables and as n (%) for categorical variables.

\*There are overlapping cases of ENBD and PTBD.

ENBD indicates endoscopic nasal biliary drainage; ERBD, endoscopic retrograde biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

evaluated using the Fisher exact test with a 2-sided significance level of 0.05.

All results were analyzed using the full analysis set, which included all patients, except for those deemed ineligible after registration. We performed a similar analysis,

using the per-protocol set as a reference. All analyses were performed using R version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria). (Supplemental Data File 5, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>).

TABLE 2. Operative and Postoperative Patients' Baseline Clinical Characteristics in the Full Analysis Set

Characteristics	Arm A (control) (n = 253)		Arm B (polyglycolic acid felt reinforcement) (n = 255)	
	N (%)	Missing value	N (%)	Missing value
Operative findings				
Operation		4		6
PD	39 (15.7)		31 (12.4)	
PPPD	120 (48.2)		128 (51.4)	
SSPPD	90 (36.1)		90 (36.1)	
PJ procedure		5		6
Mattress (Blumgart)	204 (82.3)		210 (84.3)	
Nonmattress	44 (17.7)		39 (15.7)	
Kakita	1 (2.3)		1 (2.6)	
Duct to mucosa	41 (93.2)		38 (97.4)	
End-to-side invagination	1 (2.3)		0 (0)	
No anastomosis	1 (2.3)		0 (0)	
Pancreatic stent		5		6
No	39 (15.7)		33 (13.3)	
Yes	209 (84.3)		216 (86.7)	
Internal stent	163 (78)		168 (77.8)	
External stent	46 (22)		48 (22.2)	
Operative time (min)	340.0 (86.0–937.0)	3	333.0 (115.0–720.0)	6
Blood loss (mL)	450.0 (0.0–3765.0)	3	500.0 (0.0–3530.0)	6
Blood transfusion		3		6
No	228 (91.2)		220 (88.4)	
Yes	22 (8.8)		29 (11.6)	
Pancreatic texture		5		6
Soft	226 (91.1)		224 (90)	
Hard	22 (8.9)		25 (10)	
MPD diameter (mm)	2.0 (1.0–8.0)	4	2.0 (1.0–7.0)	6
Schuh's classification		5		6
A	1 (0.4%)		1 (0.4%)	
B	21 (8.5%)		24 (9.6%)	
C	2 (0.8%)		1 (0.4%)	
D	224 (90.3%)		223 (89.6%)	
No. abdominal drains	2 (0–4)	4	2 (1–4)	6
Method of drainage		5		7
Closed	248 (100)		245 (98.8)	
Open	0 (0)		3 (1.2)	
Postoperative laboratory data				
White blood cell count (cells/mm <sup>3</sup> )				
1 postoperative day	11285 (1018–28280)	7	11410 (1117–25450)	6
3 postoperative days	10190 (1155–26150)	8	10600 (1000–30410)	6
Hemoglobin (g/dL)				
1 postoperative day	11.2 (8.2–15.7)	7	11.6 (7.9–15.2)	6
3 postoperative days	9.9 (6.5–14.4)	8	10.1 (6.7–16.8)	6
Albumin (g/dL)				
1 postoperative day	3.0 (2.0–4.4)	7	3.1 (2.1–4.1)	6
3 postoperative days	2.9 (1.4–4.0)	8	2.9 (1.7–4.1)	6
Serum amylase (IU/L)				
1 postoperative day	309 (19–2763)	8	280 (12–2468)	7
3 postoperative days	59 (4–2401)	9	61 (9–543)	6
C-reactive protein (mg/L)				
1 postoperative day	8.6 (0.5–28.7)	39	8.5 (0.1–19.6)	34
3 postoperative days	18.7 (1.4–191.4)	19	17.3 (3.1–41.9)	17
Postoperative findings				
Drain amylase concentration (IU/L)				
1 postoperative day	2572 (0–173772)	7	1926 (0–98763)	8
3 postoperative days	341 (0–37703)	9	303 (0–18267)	9
Drainage duration (d)	7 (1–73)	10	7 (3–260)	9
Postoperative stay (d)	17 (4–125)	8	15 (5–167)	7
Postoperative complications				
Pancreatic fistula		7		8
None	116 (47.2)		122 (49.4)	
All	130 (52.8)		125 (50.6)	
Biochemical leak	59 (24)		61 (24.7)	
Grade B	68 (27.6)		62 (25.1)	
Grade C	3 (1.2)		2 (0.8)	
Delayed gastric emptying		7		8

TABLE 2. (continued)

Characteristics	Arm A (control) (n = 253)		Arm B (polyglycolic acid felt reinforcement) (n = 255)	
	N (%)	Missing value	N (%)	Missing value
None	227 (92.3)		225 (91.1)	
All	19 (7.7)		22 (8.9)	
Grade A	7 (2.8)		12 (4.9)	
Grade B	8 (3.3)		7 (2.8)	
Grade C	4 (1.6)		3 (1.2)	
Intra-abdominal hemorrhage		7		8
None	236 (95.9)		238 (96.4)	
All	10 (4.1)		9 (3.6)	
Grade A	1 (0.4)		0 (0)	
Grade B	8 (3.3)		6 (2.4)	
Grade C	1 (0.4)		3 (1.2)	
Intra-abdominal abscess		7		8
No	224 (95.9)		228 (92.3)	
Yes	22 (8.9)		19 (7.7)	
Grade I	0 (0)		1 (0.4)	
Grade II	6 (2.4)		6 (2.4)	
Grade IIIa	15 (6.1)		11 (4.5)	
Grade IIIb	0 (0)		1 (0.4)	
Grade IVa	1 (0.4)		0 (0.0)	
Grade IVb	0 (0)		0 (0.0)	
Grade V	0 (0)		0 (0.0)	
Any complications		7		10
No	91 (37)		90 (36.7)	
Yes	155 (63)		155 (63.3)	
Mortality		9		11
No	241 (98.8)		243 (99.6)	
Yes	3 (1.2)		1 (0.4)	
Postoperative CT findings at 3 mo				
CT		10		11
No	29 (11.9)		31 (12.7)	
Yes	214 (88.1)		213 (87.3)	
Main pancreatic duct diameter (mm)	2.3 (0.1–29.0)		2.3 (0.1–35.0)	

Data are expressed as the median (range) for continuous variables and as n (%) for categorical variables.

Schuh's classification is based on pancreatic texture and MPD diameter: A = hard and MPD > 3 mm; B = hard and MPD ≤ 3 mm; C = soft and MPD > 3 mm; D = soft and MPD ≤ 3 mm.

CT indicates computed tomography; MPD, main pancreatic duct; PD, pancreatoduodenectomy; PJ, pancreaticojejunostomy; PPPD, pylorus-preserving pancreatoduodenectomy; SSPPD, subtotal stomach-preserving pancreatoduodenectomy.

## RESULTS

### Trial Patients

Between October 1, 2018, and December 30, 2021, 514 patients (median of 16 patients enrolled from each hospital; range 0–107) were assigned to Arm A (258 patients) or Arm B (255 patients) under randomization, except for one patient for whom data were unavailable (Fig. 2). Of these patients, 1 had no available data, 4 were found to be ineligible after enrollment, and 1 did not provide valid consent and was excluded from subsequent analyses. The full analysis population consisted of 508 patients, including 253 patients in Arm A and 255 patients in Arm B, of whom 20 patients were not treated according to the protocol due to withdrawal of consent, contraindications to resection, technical problems, noncompliance with randomization, or other reasons. The remaining per-protocol population consisted of 245 patients in Arm A and 243 patients in Arm B.

### Patients' Baseline Clinical Characteristics

The preoperative baseline clinical characteristics of the patients in both groups based on the full analysis set are

presented in Table 1. The patients' baseline characteristics, including the MPD diameter, thickness of the pancreas, and preoperative laboratory data were balanced, and there were no significant differences between the groups. The baseline clinical characteristics of the surgical and postoperative patients between the groups based on the full analysis set are shown in Table 2. The classification proposed by Schuh et al,<sup>12</sup> based on pancreatic texture and MPD diameter, was also applied as part of the baseline clinical characteristics. In terms of the operative findings, there were no significant differences in the diameter of the MPD, the pancreatic texture, or the pancreaticojejunostomy procedure between the 2 groups. There were no significant differences in any of the postoperative laboratory parameters, including the amylase concentration in the drainage fluid, between the groups. In addition, postoperative pancreatic duct diameter was assessed at 3 months postoperatively to evaluate potential anastomotic stenosis; however, no significant difference between groups was observed.

### Primary Endpoint

The primary endpoint of this trial was the incidence of grade B/C POPF, which is presented in Table 3 and

**TABLE 3.** Primary Endpoint Data for the Full Analysis Set and Per-Protocol Set

Primary endpoint	Pancreatic fistula		Adjusted OR (95% CI)	P
	Grade B/C	Incidence (%) (95% CI)		
Full analysis set			0.97* (0.90–1.05)	0.453 <sup>†</sup>
Control (Arm A) (n = 253)	71	28 (23–34)		
Treatment (Arm B) (n = 255)	64	25 (20–31)		
Per-protocol set			0.97* (0.90–1.05)	0.503 <sup>†</sup>
Control (Arm A) (n = 245)	70	29 (23–35)		
Treatment (Arm B) (n = 243)	63	23 (21–32)		

\*Adjusted odds ratios were calculated using logistic regression analysis with the suturing method used to suture the pancreas and the jejunum (mattress or nonmattress sutures) as a covariate.

<sup>†</sup>The Fisher exact test.

CI indicates confidence interval; OR: odds ratio.

Supplemental Data File 6, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>. According to the full analysis, the incidence of grade B/C POPF in Arm A was 28%, whereas that in Arm B was 25% (adjusted odds ratio: 0.97, 95% CI: 0.90–1.05;  $P=0.453$ ). Similarly, the incidence of grade B/C POPF in Arm B in the per-protocol set was 29%, and that in Arm B was 23% (adjusted odds ratio: 0.97, 95% CI: 0.90–1.05;  $P=0.503$ ). In other words, the Fisher exact test revealed no significant difference between the 2 groups regarding the incidence of grade B/C POPF after pancreaticojejunostomy.

## Secondary Endpoints

The secondary endpoint results for the full analysis set are presented in Table 4. There were no differences in the

operative time or intraoperative blood loss between the 2 groups. In Arm B, pancreaticojejunostomy with double coating of PGA felt did not cause increased bleeding or a prolonged operative time. The overall incidence of POPF was 51% in Arm A and 49% in Arm B, which was not significantly different. Similarly, there were no significant differences between the 2 groups in terms of DGE, intra-abdominal abscesses, or intra-abdominal hemorrhage. A comparison of the incidence of POPF-related complications and overall postoperative complications revealed no increase in Arm B. In addition, there were no significant differences in the length of postoperative hospital stay or readmission rate between the 2 groups. The similar results of the analysis for the per-protocol set are presented in

**TABLE 4.** Secondary Endpoint Data for the Full Analysis Set in This Study

Secondary endpoints	Arm A (control), n (%) n = 253	Arm B (polyglycolic acid felt reinforcement), n (%), n = 255	Adjusted OR (95% CI)	P
Operative time (min)	340.0 (86.0–937.0)	333.0 (115.0–720.0)	NA	0.423*
Blood loss (mL)	450.0 (0.0–3765.0)	500.0 (0.0–3530.0)	NA	0.212*
Pancreatic fistula (biochemical leak, grade B/C)	130 (51)	125 (49)	0.98 (0.90–1.07)	0.648 <sup>†</sup>
Delayed gastric emptying				
Any grade (grade A/B/C)	19 (8)	22 (8)	1.01 (0.96–1.06)	0.643 <sup>†</sup>
Grade B/C	12 (5)	10 (4)	0.99 (0.96–1.03)	0.661 <sup>†</sup>
Grade C	4 (2)	3 (1)	1.00 (0.98–1.02)	0.676 <sup>†</sup>
Intra-abdominal abscess				
Any grade (grade A/B/C)	22 (9)	19 (7)	0.99 (0.94–1.04)	0.600 <sup>†</sup>
Grade B/C	16 (6)	12 (5)	0.98 (0.94–1.02)	0.426 <sup>†</sup>
Grade C	1 (0.4)	0 (0)	NA	NA
Postpancreatectomy hemorrhage				
Any grade (grade A/B/C)	10 (4)	9 (4)	1.00 (0.96–1.03)	0.833 <sup>†</sup>
Grade B/C	9 (4)	9 (4)	1.00 (0.97–1.03)	0.978 <sup>†</sup>
Grade C	1 (0.4)	3 (1)	1.01 (0.99–1.02)	0.330 <sup>†</sup>
Drain reinsertion	43 (17)	42 (16)	1.00 (0.93–1.06)	0.895*
Postoperative complications	155 (61)	155 (61)	1.00 (0.92–1.09)	0.986*
Postoperative pancreatic fistula- related complications	137 (54)	132 (52)	0.98 (0.89–1.06)	0.576 <sup>†</sup>
Drainage duration (d)	7 (1–73)	7 (3–260)	NA	0.437*
Postoperative hospital length of stay (d)	17 (4–125)	15 (5–167)	NA	0.411 <sup>†</sup>
Reoperation	6 (2)	7 (3)	1.00 (0.98–1.03)	0.772 <sup>†</sup>
Readmission	29 (11)	33 (13)	1.02 (0.96–1.08)	0.567 <sup>†</sup>
Mortality	3 (1)	1 (0.4)	0.99 (0.98–1.01)	0.302 <sup>†</sup>

Data are expressed as the median (range) for continuous variables and as n (%) for categorical variables.

ORs and 95% CIs were calculated for all events.

\*Fisher exact test.

<sup>†</sup>Wilcoxon test.

CI indicates confidence interval; NA: not applicable; OR: odds ratio.

**TABLE 5.** Subgroup Analysis in the Full Analysis set for the Primary Endpoint (the Incidence of POPF Grade B/C)

Primary endpoint	Arm A (control), n (%) (n = 253)	Arm B (polyglycolic acid felt reinforcement) n (%) (n = 255)	OR (95% CI)	P
Anastomotic methods of PJ				
Mattress	n = 204 62 (30)	n = 210 53 (25)	0.77 (0.49–1.22)	0.273*
Nonmattress	n = 44 9 (20)	n = 39 11 (28)		
Pancreas thickness				
< 10 mm	n = 37 4 (11)	n = 35 8 (23)	2.41 (0.57–12.18)	0.214*
11–15 mm	n = 100 33 (33)	n = 120 32 (27)	0.74 (0.40–1.38)	0.373*
16–20 mm	n = 70 24 (34)	n = 49 17 (35)	0.74 (0.40–1.38)	> 0.999*
> 21 mm	n = 23 7 (30)	n = 31 4 (13)	0.35 (0.06–1.61)	0.173*
Main pancreatic duct diameter				
< 1 mm	n = 48 10 (21)	n = 48 6 (12)	0.55 (0.15–1.85)	0.412*
2 mm	n = 108 36 (33)	n = 128 39 (20)	0.88 (0.49–1.58)	0.675*
2.1–3 mm	n = 97 25 (26)	n = 79 19 (24)	0.91 (0.43–1.91)	0.862*
BMI (kg/m <sup>2</sup> )				
< 24	n = 131 36 (27)	n = 137 31 (23)	0.77 (0.43–1.39)	0.398*
> 24	n = 122 35 (29)	n = 118 33 (28)	0.97 (0.53–1.76)	> 0.999*
Primary diseases				
Benign	n = 46 13 (28)	n = 56 14 (25)	1.13 (0.42–3.02)	> 0.999*
Malignant	n = 207 58 (28)	n = 199 50 (25)	1.17 (0.73–1.87)	> 0.999*
Preoperative biliary drainage				
No	n = 103 30 (29)	n = 114 27 (24)	0.76 (0.39–1.45)	0.44*
Yes (internal)	n = 124 34 (27)	n = 115 32 (28)	1.02 (0.56–1.87)	> 0.999*
Yes (external)	n = 37 10 (27)	n = 37 9 (24)	0.87 (0.27–2.80)	> 0.999*
Pancreatic stent				
No	n = 39 15 (38)	n = 33 11 (33)	0.80 (0.27–2.34)	0.806*
Yes (internal stent)	n = 163 32 (20)	n = 168 34 (20)	1.04 (0.58–1.85)	> 0.999*
Yes (external stent)	n = 46 24 (52)	n = 48 19 (40)	0.60 (0.24–1.47)	0.301*

Data are expressed as the median (range) for continuous variables and as n (%) for categorical variables.

ORs and 95% CIs were calculated for all events.

\*Fisher exact test.

BMI indicates body mass index; CI, confidence interval; NA, not applicable; OR, odds ratio; PJ, pancreaticojejunostomy; POPF, postoperative pancreatic fistula.

Supplemental Data File 7, Supplemental Digital Content 1, <http://links.lww.com/SLA/F553>.

### Additional Analysis

In addition, subgroup analysis was performed for the incidence of POPF grade B/C as the primary endpoint. Table 5 shows the incidences of grade B/C POPF in the subgroups. No significant difference in the incidence of grade B/C POPF was observed for patients with different pancreaticojejunostomy methods, pancreatic thicknesses, MPD diameters, BMIs > 24 kg/m<sup>2</sup>, primary diseases, preoperative biliary drainage, or pancreatic duct stenting.

### DISCUSSION

PD is an advanced procedure that requires a high-level surgical technique. With advances in surgical techniques and perioperative care, mortality has decreased to < 5%. However, POPF remains a frequent complication, often causing intra-abdominal bleeding or abscesses.<sup>1–10</sup> In addition, various management methods have been reported to reduce the incidence of perioperative complications.<sup>32–37</sup>

The aim of this study was to evaluate the usefulness of a method using double coating of PGA felt for pancreaticojejunostomy in patients with a normal pancreas undergoing PD in reducing the incidence of grade B/C POPF as a

cause of subsequent severe complications. A double-layer PGA felt technique was employed based on anatomic and material-specific considerations. We considered that pancreatic fistulas require countermeasures against both leakage from the pancreatic jejunal anastomosis itself and leakage from a needle hole that penetrates the pancreas. For the former, thin PGA felt (0.15 mm) was used because it is more flexible and better conforms to the complex 3-dimensional structure of the anastomotic site. For the latter, a thicker PGA felt (0.3 mm) was applied to both the ventral and dorsal surfaces of the pancreas to ensure firm coverage and support.

The primary endpoint demonstrated that the incidence of grade B/C POPF of 25% in the novel treatment group was comparable to that of 28% in the conventional group ( $P=0.453$ ). Contrary to our expectations, our hypothesis that double-coating PGA anastomosis might reduce the incidence of grade B/C POPF was not confirmed.

The secondary endpoints also showed no significant differences in short-term outcomes, including the incidence of overall biochemical leak and POPF, PPH, the duration of postoperative drainage, and the length of postoperative hospital stay. Notably, the incidence of intra-abdominal abscesses and mortality were also not significantly different between the 2 groups. This finding suggested that PGA felt may not contribute to abscess formation even in environments exposed to digestive fluids. We believe that reinforcement by PGA felt is possible in the gastrointestinal surgical field, including for pancreatic surgery. Previous retrospective studies reported that the use of PGA felt during pancreaticojejunostomy reduced the incidence of POPF.<sup>29,38,39</sup> Regarding distal pancreatectomy, wrapping the cut surface of the pancreas with PGA mesh reduced the incidence of POPF in prospective studies.<sup>40</sup> Furthermore, ongoing prospective studies, such as the WRAP trial, are addressing this issue by investigating the application of a double layer of PGA felt to the pancreatic stump following distal pancreatectomy.<sup>41</sup> The use of PGA felt during pancreatic surgery is still considered safe and effective in reducing the incidence of postoperative complications.

On the other hand, no significant difference was found in other studies.<sup>30,42</sup> It has been reported that PGA mesh may not work effectively due to uneven anastomosis between the solid organ and the intestine, which may prevent appropriate coverage of these junctions. As a result, when POPF develops at the anastomotic site, the area reinforced by the PGA felt may gradually weaken as a space is created between the PGA felt and the anastomosis.<sup>30,39</sup>

In recent years, with the development of novel preoperative and postoperative chemotherapies, the prognosis for patients with pancreatic cancer has improved.<sup>43–47</sup> The initiation of adjuvant chemotherapy without delay is essential to prolong the survival of pancreatic cancer patients. To this end, efforts to reduce complications, including pancreatic fistula, are necessary.

We have participated in several multicenter prospective randomized trials in the field of pancreatic surgery.<sup>48,49</sup> In this study, the hypothesis that the incidence of pancreatic fistulas would be reduced was rejected unfortunately, but this study did contribute to confirming the safety of PGA felt. The inclusion of more than 500 patients (limited to patients with a normal pancreas) is a

major step forward in pancreatic surgery, and further investigations are expected in the future.

This study has several limitations associated with its multi-institutional design. First, the technique for attaching the first PGA felt to the pancreaticojejunostomy may have been complicated. The soft pancreas is a very fragile tissue that requires great care during pancreaticojejunostomy needle placement. As a result, the intervention may not have been properly integrated. Second, drain management was left to the discretion of the surgeon or the style of each institution. The fashion for changing and even removing drains in patients with high drainage fluid amylase levels may vary among individual institutions and primary surgeons. Postoperative drainage fluid with high amylase levels must be carefully managed to prevent complications, and uniformity in drain management practices may be life-threatening to patients. Therefore, detailed drain management regulations were not established for ethical reasons.

In conclusion, pancreaticojejunostomy performed using a double coating of PGA felt in this study did not reduce the incidence of grade B/C POPF.

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