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Risk Factors for Pancreatic Fistula Following Distal Pancreatectomy

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ABSTRACT

Introduction: Distal pancreatectomy (DP) is a standard treatment for pancreatic cancer and cystic disease of the distal pancreas. Advances in laparoscopic surgery and stapling devices have led to increased use of staplers in DP; however, the incidence of postoperative pancreatic fistulas (PF) remains high. Here, we investigated the risk factors for PF following DP.

Methods: Medical record data were used to retrospectively investigate the risk factors for PF in all 131 patients in which DP was performed at our hospital from January 2008 to December 2020, including 85 patients in which only staplers were used.

Results: Multivariate analysis showed that the following were independent risk factors for PF: pancreatic thickness ≥ 15 mm (adjusted odds ratio [OR], 2.98; 95% confidence interval [CI], 1.27-7.00), operation time ≥ 350 min (OR, 2.60; 95% CI, 1.10-6.14), and without reinforcing material (OR, 3.24; 95% CI, 1.14-9.23). Among those for whom only staplers were used, the independent risk factors were pancreatic thickness of ≥ 14 mm (OR, 3.40; 95% CI, 1.17-9.87) and without reinforcing material (OR, 3.04; 95% CI, 1.11-8.35). Especially, the pancreatic thickness and/or bleeding volume were risk factors in black and reinforced stapler group.

Conclusions: The thickness of the pancreas may be a risk factor for PF, and the incidence of PF could be reduced using staplers with a black cartridge and a reinforcing material in pancreatectomy when the pancreas is ≤ 14 mm in thickness and the bleeding volume is < 750 mL.

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KEYWORDS: pancreatic fistula, distal pancreatectomy, pancreatic neoplasms, stapler

Introduction

Distal pancreatectomy (DP) is mainly performed for pancreatic cancer and cystic disease of the distal pancreas. To date, fish-mouth closure has been used for stump closure after DP, but the development of stapling devices has

resulted in the use of these staplers for pancreatectomy as well. Advances in laparoscopic surgery and stapling devices since then have increased the opportunities for stapler use; however, the incidence of postoperative pancreatic fistulas (PF) remains high¹⁾ and is a serious persistent complication. A report on pancreatic stump closure indi-

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cated that there were no differences in the frequency of PF occurrence between closure using a stapler alone and closure by stump suturing;²⁾ however, it was subsequently reported that PF occurrence was greatly reduced by adding a reinforcing material to the stapler in pancreatectomy,³⁾ and it is presently believed that stapler use is a highly safe approach. The risk factors for PF include age, body mass index (BMI), and surgical factors such as pancreatic thickness and hardness.⁴⁾ In 2001, we introduced a method of pancreatectomy that employed stapling devices.⁵⁾ We initially performed additional suturing to the pancreas stump for reinforcement, but we still had some cases of PF. Therefore, we hypothesized that the type of stapler and preoperative factors were risk factors for PF. Here, we investigated the risk factors for PF following DP.

Methods

The subjects were 131 patients who underwent DP from January 2008 to December 2020 at Toho University Medical Center Omori Hospital. Various pancreatectomy methods were used, including those involving the use of a scalpel, an ultrasonically activated device (UAD), and a stapler. Medical record data were used to retrospectively investigate the risk factors for PF in all 131 patients, including 85 patients in which only a stapler was used. The definition of PF was Grade B/C cases according to the 2016 International Study Group Pancreatic Fistula diagnostic criteria.⁶⁾ Regarding PF diagnosis, any measurable volume of drain fluid on or after postoperative day 3 with an amylase level of >3 times the upper limit of normal amylase for each institution was considered a necessary threshold. Grade B was defined as persistent drainage that extended for 3 weeks, repositioned through endoscopic or percutaneous procedures, angiographic procedure for bleeding, or signs of infection without organ failure. Grade C refers to the cases of postoperative PF that require reoperation or lead to single or multiple organ failure and/or mortality attributable to the PF.

Investigated patient factors included age, BMI, presence or absence of underlying disease (diabetes with oral or insulin treatment history, ischemic heart disease, cerebral infarction, chronic renal failure, history of pancreatitis, and use of oral anticoagulants or steroids), surgical diagnosis, and benign or malignant disease status. Surgical factors investigated included thickness of the pancreatic parenchyma at the pancreatectomy site and hardness of the pancreas. Other factors included presence or absence of la-

paroscopic surgery; complications in surgery other than in the pancreas; pancreatectomy method; stapler type; cartridge type; additional suturing of the pancreatic stump; operation time; bleeding volume; intraoperative blood transfusion; presence or absence of PF; and length of hospital stay. Benign or malignant status was judged based on the postoperative pathology, and the thickness of the pancreas was measured using preoperative computed tomography images. The evaluation of pancreatic hardness was based on the subjective assessment of the surgeon, as documented in the operative notes, and was not confirmed histologically. When performing pancreatectomy using a stapler, we performed compression in advance to avoid damaging the pancreatic capsule [slowly conducted compression over a period of at least five min⁷⁾] and operated in a protective manner by conducting the dissection after thinly flattening the pancreatic dissection line.

Statistical analysis

Continuous data were expressed using the median and range. For the statistical analyses, the chi-square test was used to compare categorical variables, and nonparametric tests (Mann-Whitney *U* test) were used to compare continuous variables. The optimum cutoff value was determined using the receiver operating characteristic (ROC) curve, and the sensitivity, specificity, and area under the curve (AUC) were determined. Multivariate analysis was performed using multiple logistic regression analysis, and P-values of less than 0.05 were considered statistically significant.

Results

Patients' disease

The disease conditions for which DP was performed are presented in Table 1; 110 cases of pancreatic disease, 11 cases of stomach disease, and 10 cases of other diseases were evaluated.

Details of the surgical factors

The surgical factors and results of pancreatectomies are detailed in Table 2. The median pancreatic thickness was 14.0 (7-27) mm, and the pancreases of 23 cases (17.6%) were deemed hard. Laparoscopic surgery was conducted in 42 cases (32.1%). Resection of other organs such as the stomach, bowel, or rectum was conducted in 27 cases (20.6%). The pancreatectomy method involved incision using a scalpel or UAD and additional suturing; the pancreatic stump was hand-sewn in 15 cases and stapled in 116 cases. Of the patients in which a stapler was used, 85 involved

Table 1 Patient's disease

PDAC	48
MCN	14
NEN	13
IPMN	13
Chronic pancreatitis	10
Stomach cancer	10
SCN	5
Splenic tumor	5
SPN	4
Pancreatic trauma	2
Portal hypertension	2
Metastatic pancreas tumor	1
GIST of stomach	1
Splenic artery aneurysm	1
Adrenal gland tumor	1
Lymphoma of spleen	1

PDAC: Pancreatic Ductal Adenocarcinoma. MCN: Mucinous Cystic Neoplasm. NEN: Neuroendocrine Neoplasm. IPMN: Intraductal Papillary Mucinous Neoplasm. SCN: Serous Cystic Neoplasm. SPN: Solid Pseudopapillary Neoplasm. GIST: Gastrointestinal Stromal Tumor.

dissection with only the stapler; 27 involved reinforcement of the stump with additional sutures; and 4 involved superficial flattening of the thick and hard pancreatic parenchyma using a UAD, with subsequent cutting and closure of the stump using a stapler. In all, 42 (32.1%) cases involved additional suturing for stump reinforcement following pancreatectomy, which combined hand-sewn suturing with the use of a stapler. Another 12 cases required additional resection of the pancreatic parenchyma because the pancreatic margin was positive for cancer cells on frozen sections. The staplers used were the following: PROXIMATE[®] TL (Ethicon Endo-Surgery, Cincinnati, OH, USA), 8 cases; Duet TRS[™] (Covidien Medtronic, Minneapolis, MN, USA), 2 cases; ECHELON FLEX[™] ENDOPATH[®] (Ethicon Endo-Surgery), 46 cases; and End-GIA[™] (Covidien Medtronic), 60 cases. Tri-staple[™] 2.0 Reinforce[®] was used in 48 of the 60 cases. The stapler cartridges that were selected included white, blue, purple, gold, green, and black colored cartridges. The reinforcing material group comprised the 50 cases in which either Duet TRS[™] or Tri-staple[™] 2.0 Reinforce[®] was used. Regarding the surgical record, the median intraoperative bleeding volume was 535 (0-5618) mL and the median operating time was 349 (145-651) min.

Postoperative PF was observed in 52 cases (39.7%). The breakdown of PF was as follows: Grade B, 48 cases; Grade

C, 4 cases; mortality, 1 case. The median postoperative hospital stay was 25 (7-166) days.

The stapler and PF

The stapler used two or three rows of staple lines. PROXIMATE[®] TL was the two-row stapler; and Duet TRS[™], ECHELON[™], and Tri-staple[™] were the three-row stapler. The staple heights as per the manufacturer's description after the stapler closure are as follows: TL, 1.0-2.5 mm; white, 1.0 mm; blue, 1.5 mm; gold, 1.8 mm; green, 2.0 mm; and black, 2.3 mm. The heights for the Tri-staple[™] were as follows: purple, 1.5-2.25 mm; and black, 2.25-3.0 mm. Additional sutures were placed for stump reinforcement following pancreatectomy for all patients in which a two-row stapler and white cartridges were used. Additional sutures were also used in 27 cases (23.3%); however, no additional sutures were performed in any cases in which purple sutures were used. Analyzing the thickness of the pancreatic parenchyma that was excised according to the cartridge used showed that the pancreatic parenchyma tended to be thicker for purple, gold, and green cartridges; and thinner for higher staples (white, blue, and black cartridges). The PF frequency was low for black cartridge use, at 15 cases (26.8%) (Table 3).

Risk factors for PF

All patients were divided into two groups according to the presence or absence of PF, and the relationship between PF and preoperative and intraoperative factors was analyzed. Preoperative factors, including sex, diabetes, and history of pancreatitis, tended to be associated with a higher incidence of PF, but this was not statistically significant; other factors were not significantly associated with PF.

Intraoperative factors tended to be associated with a higher incidence of PF, including the texture of the pancreatic parenchyma and additional suturing of the pancreatic stump, but this association was not significant. There was no significant difference regarding the types of staplers used (two-rows vs. three-rows) between the groups. There were significant differences in pancreatic thickness between the groups for the following: DP with other surgeries, use of stapler only, use of reinforcing material, operation time, bleeding volume, presence or absence of blood transfusion, and length of hospital stay (Table 4). The cutoff values according to the ROC curve were as follows: pancreatic thickness, 14 mm (sensitivity, 52.6%; specificity, 82.1%; AUC, 0.696); operation time, 349 min (sensitivity, 71.7%; specificity, 63.3%; AUC, 0.639); and bleeding vol-

Table 2 Details of the surgical results

		All patients (n = 131)	Stapler only (n = 85)
Pancreas parenchyma	Thickness	14.0 (7-27) mm	14.0 (7-27) mm
	Texture Soft/Hard	108/23 (82.4%/17.6%)	78/7 (91.8%/8.2%)
Procedure of DP	Open/Lap	89/42 (67.9%/32.1%)	48/37 (56.5%/43.5%)
	DP with other surgeries	27 (20.6%)	12 (14.1%)
Pancreas resection	Hand sewn	15 (11.5%)	–
	Stapler	116 (88.5%)	85
	Only stapler/with suture/with UAD	85/27/4	85/–/–
Stapler type	Additional resection	12 (9.2%)	6 (7.1%)
	2-row/3-row	8/108	0/85
Cartridge	TL/Duet-TRS/Echelon/Tri-staple	8/2/46/60	0/2/31/52
	White/Blue/Purple/Gold/Green/Black	2/8/4/7/31/56	0/0/5/3/3/23/51
Result of the surgery	Reinforcing material	50 (43.5%)	49 (57.6%)
	Bleeding volume	535 (0-5618) mL	535 (0-3950) mL
	Operation time	349 (145-651) min	350 (145-651) min
Morbidity	Blood transfusion	28 (33.7%)	20 (23.5%)
	PF	52 (39.7%)	28 (32.9%)
	Grade B/C	48/4	26/2
	Mortality	1 (0.8%)	1 (1.2%)
	Hospital stay	25 (7-166) day	20 (7-135) day

DP: Distal Pancreatectomy. Lap: Laparoscopic Surgery. UAD: Ultrasonically Activated Device. Hand sewn: Blade or/and UAD with Suture. PF: Pancreatic Fistula.

Table 3 Relation between the stapler cartridge and pancreatic fistula

Cartridge (n)	TL 8	White 2	Blue 8	Purple 4	Gold 7	Green 31	Black 56
Staple line	2-row	3-row	3-row	3-row	3-row	3-row	3-row
Products	TL	Echelon	Echelon, Duet	Tri-staple	Echelon	Echelon	Tri-staple, Echelon
Staple height after firing † (mm)	1.0-2.5	1.0	1.5	1.5-2.25	1.8	2.0	2.25-3.0
Additional suture	8 (100%)	2 (100%)	3 (37.5%)	0 (0%)	4 (57.1%)	8 (25.8%)	2 (3.6%)
Thickness of the pancreas (median mm/ range)	16 (13-22)	16 (12-20)	14.0 (10-20)	13.0 (7-23)	15.0 (12-21)	16.0 (10-22)	13.0 (7-27)
PF	4 (50%)	0 (0%)	5 (62.5%)	1 (25%)	3 (42.9%)	16 (51.6%)	15 (26.8%)

† Staple heights as per the manufacturer's description after the stapler closure.

ume, 500 mL (sensitivity, 71.7%; specificity, 54.4%; AUC, 0.634). Multivariate analysis showed the following as independent risk factors for PF: pancreatic thickness ≥ 15 mm (adjusted odds ratio [OR], 2.98; 95% confidence interval [CI], 1.27-7.00), operation time ≥ 350 min (OR, 2.60; 95% CI, 1.10-6.14), and absence of reinforcing material (OR, 3.24; 95% CI, 1.14-9.23) (Table 5).

Risk factors for PF when a stapler alone was used (n = 85)

PF was observed in 28 cases in this group (32.9%) (Table

2). In the univariate analysis, pancreatic thickness, reinforcing material, and operation time were significant risk factors for PF. The cutoff values according to the ROC curve were as follows: pancreatic thickness, 13 mm (sensitivity, 82.1%; specificity, 52.6%; AUC, 0.69); and operation time, 351 min (sensitivity, 71.4%; specificity, 61.4%; AUC, 0.581). Multivariate analysis revealed the following as independent risk factors: pancreatic thickness ≥ 14 mm (OR, 3.40; 95% CI, 1.17-9.87) and without the reinforcing material (OR, 3.04; 95% CI, 1.11-8.35) (Table 6).

Table 4 Patients' risk factors for pancreatic fistula

		PF (-) n = 79	PF (+) n = 52	P-value
Preoperative factors				
Age	Median year	67 (23-87)	65 (25-79)	0.53
Sex	Male (n = 63)	52.4%	47.6%	0.07
	Female (n = 68)	67.6%	32.4%	
BMI	Median kg/m ²	22.4 (15.5-33.0)	22.5 (17.1-32.7)	0.90
DM	(-) (n = 85)	54.1%	45.8%	0.05
	(+) (n = 46)	71.7%	28.3%	
IHD	(-) (n = 120)	59.2%	40.8%	0.38
	(+) (n = 11)	72.7%	27.3%	
CI	(-) (n = 122)	59.8%	40.2%	0.69
	(+) (n = 9)	66.7%	33.3%	
CRF	(-) (n = 124)	61.3%	38.7%	0.33
	(+) (n = 7)	42.9%	57.1%	
History of pancreatitis	(-) (n = 93)	65.6%	34.4%	0.05
	(+) (n = 38)	47.4%	52.6%	
Anticoagulant	(-) (n = 111)	61.3%	38.7%	0.60
	(+) (n = 20)	55.0%	45.0%	
Steroid use	(-) (n = 126)	61.1%	38.9%	0.34
	(+) (n = 5)	40.0%	60.0%	
Disease	Pancreas (n = 110)	62.7%	37.3%	0.19
	Others (n = 21)	47.6%	52.4%	
	PDAC or Pancreatitis (n = 56)	66.1%	33.9%	
	Others (n = 75)	56.0%	44.0%	
Malignancy	Benign (n = 58)	56.9%	43.1%	0.48
	Malignant (n = 73)	63.0%	37.0%	
Intraoperative factors				
Pancreas thickness	Median (mm)	13.0 (7-27)	16.0 (9-25)	<0.01
Texture	Soft (n = 108)	63.9%	36.1%	0.07
	Hard (n = 23)	43.5%	56.5%	
Operation	Open (n = 89)	56.2%	43.8%	0.16
	Lap (n = 42)	69.0%	31.0%	
DP with other surgeries	(-) (n = 104)	65.4%	34.6%	0.02
	(+) (n = 27)	40.7%	59.3%	
Resection	Only stapler (n = 85)	67.4%	32.6%	0.03
	Others * (n = 46)	46.7%	53.3%	
Additional suture	(-) (n = 89)	65.2%	34.8%	0.10
	(+) (n = 42)	50.0%	50.0%	
Additional resection	(-) (n = 119)	60.5%	39.5%	0.88
	(+) (n = 12)	58.3%	41.7%	
Staple line	2-row (n = 8)	55.6%	44.4%	0.68
	3-row (n = 108)	62.6%	37.4%	
Stapler cartridge	Black (n = 56)	73.2%	26.8%	0.02
	Others (n = 60)	51.7%	48.3%	
Reinforcing material	(-) (n = 81)	49.4%	50.6%	<0.01
	(+) (n = 50)	78.0%	22.0%	
Bleeding volume	Median (mL)	405 (0-5618)	727 (0-4310)	0.01
Operation time	Median (min)	327 (166-651)	382 (145-568)	0.01
Blood transfusion	(-) (n = 92)	67.4%	32.6%	0.01
	(+) (n = 39)	43.6%	56.4%	
Hospital stay	Median day	15 (7-166)	39 (14-135)	<0.01

PF: Pancreatic Fistula. BMI: Body Mass Index. DM: Diabetes Mellitus. IHD: Ischemic Heart Disease. CI: Cerebral Infarction. CRF: Chronic Renal Failure. Lap: Laparoscopic Surgery. PDAC: Pancreatic Ductal Adenocarcinoma. DP: Distal Pancreatectomy. P-values were determined using the Mann-Whitney *U* or the chi-square test.

*Hand-sewn or stapler closure with suture for reinforcement.

Table 5 Multivariate analysis for risk factors of pancreatic fistula (n = 131)

Category of risk factor	Variables	Logistic regression analysis		
		P-values	Adjusted odds ratio	95% CI
DP with other surgeries	(+) vs. (-)	0.87	0.91	0.30-2.82
Resection	Stapler vs. others	0.68	0.80	0.27-2.33
Pancreas thickness	≤14 vs. ≥15 mm	0.01	2.98	1.27-7.00
Reinforcing material	(+) vs. (-)	0.03	3.24	1.14-9.23
Bleeding volume	≤500 vs. ≥501 mL	0.13	2.36	0.78-7.11
Operation time	≤349 vs. ≥350 min	0.03	2.60	1.10-6.14

DP: Distal Pancreatectomy. CI: Confidence Interval. P-values were determined using logistic regression analysis.

Table 6 Risk factors for pancreatic fistula according to only stapler use (n = 85)

Category of risk factor	Variables	P-values		Logistic regression analysis	
		Uni-	Multi-	Adjusted odds ratio	95% CI
Disease	Pancreas vs. others	0.28			
Pancreas thickness	≤13 vs. ≥14 mm	<0.01	0.02	3.40	1.17-9.87
Texture	Soft vs. Hard	0.16			
Operation	Open vs. Lap	0.31			
DP with other surgeries	(+) vs. (-)	0.49			
Additional resection	(+) vs. (-)	0.36			
Stapler cartridge	Black vs. others	0.05			
Reinforcing material	(+) vs. (-)	0.02	0.03	3.04	1.11-8.35
Bleeding volume	≤750 vs. ≥751 mL	0.05			
Operation time	≤351 vs. ≥352 min	0.01	0.06	2.70	0.96-7.55
Blood transfusion	(+) vs. (-)	0.06			

DP: Distal Pancreatectomy. Lap: Laparoscopic Surgery. CI: Confidence Interval. P-values were determined with the chi-square test for univariate analysis and logistic regression analysis for multivariate analysis.

Risk factors for PF with a black or reinforced cartridge stapler

PF was observed in 15 (26.8%) of 56 patients using black cartridge stapler and 11 (22.0%) of 50 patients using reinforced cartridge stapler, respectively (Table 4). The characteristics of the PF patients with black and reinforcing material stapler showed that although there was no significant difference in preoperative factors, the pancreatic thickness was significantly greater in both groups. In addition, the bleeding volume was significantly higher in the patients in the black cartridge group. The incidence of PF tended to be low in patients with pancreatic cancer or pancreatitis, but the difference was not significant (Table 7). Histological examination of the pancreatic stump in PF cases showed that among the patients with pancreatic cancer, there were patients where the background pancreatic tissue architecture was well preserved, while there were also patients where the exocrine glands were atrophied and pancreatic tissue was replaced to fat. No signifi-

cant findings related to PF were obtained in histologically.

Discussion

Despite recent advances in surgical techniques and perioperative management, the incidence of PF after DP remains high (10%-40%), and it is a problematic complication because of its association with prolonged postoperative hospital stay and increased perioperative mortality.^{1,4,8)} Options for dissecting the pancreatic parenchyma include using a scalpel followed by either hand-sewn or stapler closure. A large-scale randomized controlled trial (RCT) that compared both methods (DISPACT trial) ruled out the superiority of the stapler to hand-sewn suture and closure,²⁾ however, staplers remain widely used in the clinic, including in laparoscopic surgery, due to the ease of the operation.⁹⁾

We used a two-row stapler when we introduced staplers to DP in our department, and we placed additional sutures for reinforcement. Additional sutures were subsequently

Table 7 Risk factors for PF with black or reinforced cartridge stapler

	Black stapler (n = 56)			Reinforced stapler (n = 50)		
	PF (-) (n = 41)	PF (+) (n = 15)	P-value	PF (-) (n = 39)	PF (+) (n = 11)	P-value
Preoperative factors						
Age	68 (23–87)	69 (25–79)	0.78	68 (23–87)	67 (51–78)	0.57
Sex (male)	39.0%	66.7%	0.07	35.9%	63.6%	0.10
BMI	22.1 (15.8–33.0)	23.4 (19.2–32.7)	0.36	22.6 (15.8–33.0)	22.8 (19.2–32.7)	0.77
DM	46.3%	33.3%	0.38	48.7%	45.5%	0.85
IHD	7.3%	0.0%	0.28	7.7%	0.0%	0.34
CI	12.2%	6.7%	0.55	15.4%	9.1%	0.60
CRF	4.9%	6.7%	0.79	5.1%	9.1%	0.63
History of pancreatitis	14.6%	26.7%	0.30	15.4%	18.2%	0.82
Anticoagulant	17.1%	20.0%	0.80	20.5%	27.3%	0.63
Steroid use	4.9%	0.0%	0.38	5.1%	0.0%	0.44
PDAC or Pancreatitis	43.9%	33.3%	0.48	51.3%	27.3%	0.16
Malignancy	56.1%	53.3%	0.85	59.0%	54.5%	0.79
Intraoperative factors						
Pancreas thickness	12.0 (7–27)	15.0 (9–25)	0.04	12.0 (7–27)	15.0 (9–25)	0.03
Texture (Hard)	4.9%	20.0%	0.08	2.7%	9.1%	0.33
Operation (Lap)	51.1%	33.3%	0.23	46.2%	27.3%	0.26
DP with other surgeries	9.8%	20.0%	0.30	12.8%	18.2%	0.65
Additional suture	4.9%	0.0%	0.38	7.7%	0.0%	0.34
Additional resection	7.3%	13.3%	0.48	7.7%	18.2%	0.31
Reinforcing material	87.8%	73.3%	0.19	–	–	–
Blood loss	300 (0–2490)	758 (125–2590)	0.03	327 (0–2575)	758 (125–2590)	0.11
Open duration	327 (166–651)	382 (145–568)	0.14	310 (169–651)	371 (145–501)	0.29
Blood transfusion	14.6%	33.3%	0.12	17.9%	27.3%	0.49

PF: Pancreatic Fistula; BMI: Body Mass Index; DM: Diabetes Mellitus; IHD: Ischemic Heart Disease; CI: Cerebral Infarction; CRF: Chronic Renal Failure; Lap: Laparoscopic Surgery; PDAC: Pancreatic Ductal Adenocarcinoma; DP: Distal Pancreatectomy. P-values were determined using the Mann-Whitney U or the chi-square test.

added to the three-row stapler as well, but we frequently observed PF, and we hypothesized that the type of stapler and other preoperative factors could be risk factors for PF. It has been reported that two-row stapler¹⁰⁾ and hand-sewn closures¹¹⁾ are risk factors for PF; however, the present study showed that although the rate of PF tended to be higher in patients where two-row staplers were used compared with those with three-row staplers, there was no significant difference. PF was also observed in 50% of the 42 cases with additional sutures, but there was no significant difference in PF occurrence between this group and the group without any additional sutures. PF was significantly lower in patients who underwent pancreatectomy with only a stapler. We consider that the occurrence of PF may be prevented by simply conducting pancreatectomy in a protective manner using the stapler rather than by placing additional sutures in the pancreatic parenchyma, which may increase the risk of pancreatic juice

leakage from the needle holes.

Kondo et al.¹²⁾ performed an RCT that compared a reinforced stapler that uses a cartridge equipped with polyglycolic acid (NEOVEIL[®]; Gunze Medical Japan, Osaka, Japan) with a conventional stapler (bare stapler). Analysis of its subgroups showed that cases where the thickness of the pancreatectomy section was 14 mm or less had significantly lower rates of PF occurrence, and at present, using a reinforced stapler is the safest solution to obtain a thin pancreatic parenchyma.¹³⁾ Many studies have reported that the thickness and hardness of the pancreas are risk factors for PF.^{14–18)} In this study, pancreatic thickness was an independent risk factor. Our findings suggest that PF occurrence could be reduced by using a stapler that uses a black cartridge with reinforcing material for pancreatectomies with a thickness of 14 mm or less (Fig. 1A, B, C). It has also been reported that PF is greatly reduced by adding reinforcing material to the stapler,³⁾ but in this study,

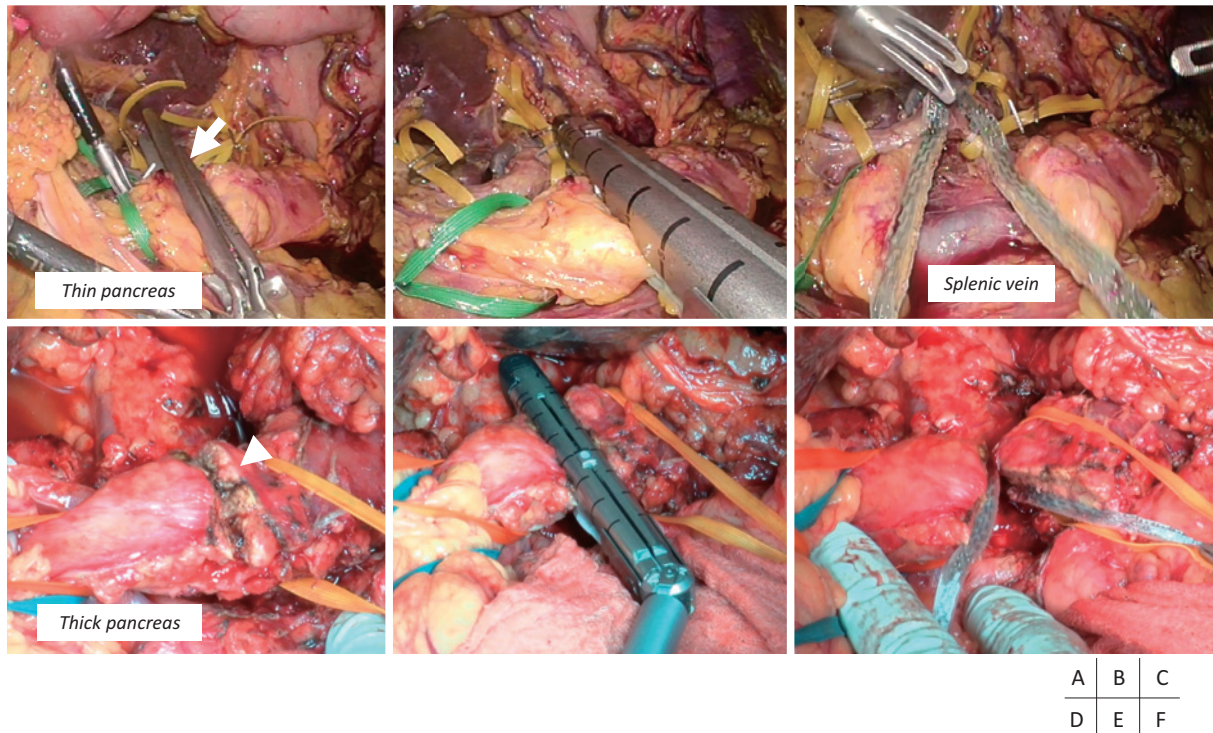


Fig. 1 Distal pancreatectomy of thin and thick pancreases.

Upper figure: Laparoscopic distal pancreatectomy of thin pancreas for pancreatic cancer. Lower figure: Distal pancreatectomy of thick pancreas; type 3b pancreatic injury due to traffic trauma.

A: Compression in advance for the resection line using an intestinal clip (white arrow). B: The stapler closed using the black and reinforced cartridge. C: After pancreatic parenchymal transection.

D: After the depth of the main pancreatic duct is determined using intraoperative ultrasound, the ventral pancreatic surface is dissected with an ultrasonic coagulation device (arrowhead). E: the main pancreatic duct is securely closed on the dorsal side using a reinforced stapler. F: After pancreatic parenchymal transection.

PF was observed in 26.8% and 22% of the patients despite the use of a black cartridge or reinforcing material stapler, respectively. PF cases for each cartridge were characterized by a thicker pancreas (15 vs. 12 mm) (Table 7). In addition, the bleeding volume was also significantly higher in the black cartridge patients (758 vs. 300 mL). It seems that even if a black cartridge with reinforcing material was used, sufficient caution would be required for PF in cases when the pancreatic thickness was ≥ 15 mm and surgery with a bleeding volume of ≥ 750 mL. Okano et al.¹⁹⁾ found infectious complications in 426 (25.2%) of 1692 DP patients and identified prolonged operation time and intraoperative blood transfusion as risk factors. PF is associated with infectious complications; accordingly, risk factors for PF in the present study were operation time, bleeding volume, presence or absence of intraoperative blood transfusion, and DP accompanied by surgery that may involve contamination by digestive juices (such as colorectal resection and gastrectomy).

Pancreatic capsule and parenchymal damage are thought to be major risk factors for PF when using staplers for resection of thick and hard pancreases. The incidence of PF in this study was low not only for black cartridges but also for white and purple cartridges. White and purple cartridges were originally intended for use in thin tissues, and as a result, PF was fortunately infrequent.

In this study, pancreatectomy with UAD and a stapler was conducted in four patients for thick and hard pancreases after pancreatic trauma or chronic pancreatitis (Fig. 1 D, E, F). Of these, two patients developed Grade B PF, but there were no serious complications. This procedure takes into account that the main pancreatic duct in the distal pancreas is located slightly dorsally.²⁰⁾ After the depth of the pancreatic duct is determined using intraoperative ultrasound, the ventral side of the pancreatic duct is sealed by ultrasonic coagulation²¹⁾ and the main pancreatic duct is securely closed on the dorsal side using the stapler. The incidence of PF could be reduced using a simple method

other than open or laparoscopic surgery, but PF cannot be sufficiently prevented at present. It has also been reported that the combined use of gastrointestinal anastomoses²²⁾ as well as covering the pancreatic stump with a mesh and placing a mattress suture²³⁾ were useful for patients with thick pancreatic parenchyma. We believe that preparation of unique dissection methods for thick pancreatic parenchyma at each institution is important, but a useful method that can reliably prevent PF will hopefully emerge in the near future.

BMI and age have been reported as preoperative patient risk factors for PF,⁴⁾ but there were no significant differences in age or BMI among those with PF in this study, and the incidence of PF tended to be low in patients with diabetes. Although not reflected in clinical and histological findings, patients with diabetes have been reported to have decreased pancreatic exocrine function,²⁴⁾ and the pancreatic secretory capacity may be further decreased following DP.²⁵⁾ The Fistula Risk Score proposed by Carley et al.²⁶⁾ derives its predictive accuracy from the findings that patients with soft pancreatic parenchyma, non-pancreatic cancer or nonpancreatitis, and normal pancreatic function with a small pancreatic duct diameter have a higher PF risk. The PF frequency in patients with pancreatic cancer or pancreatitis was not significantly different from that in patients with other diseases in this study (Table 4). Furthermore, similar results were obtained in patients where a black cartridge or a cartridge combined with a reinforcing material was used (Table 7). Histologically, the background architecture of the pancreas was preserved in some patients, but in others, the exocrine glands were atrophied, and no significant findings were obtained regarding the cause of PF. It has also been reported that the presence of fibrotic tissue increases PF,¹⁷⁾ whereas soft normal pancreatic tissue has been reported to be a risk factor for PF,^{27, 28)} and the relationship between pancreatic function and PF is controversial.

Limitations of the study

A limitation of this study is that there were no clear criteria for selecting cartridges for the stapler, and they were arbitrarily selected by the surgeons. Furthermore, this was a retrospective study, and there is a potential selection bias. We believe that hard pancreas in particular was not a risk factor because a decision of not using the stapler was made early. In the case of pancreatic sclerosis, the degree of pancreatic fibrosis is considered to be important. In this study, however, the pancreatic hardness was based on

the subjective assessment of the surgeon, so the evaluation may be biased. Further histological validation and a larger sample size may clarify the relationship between the fibrotic state of the pancreatic parenchyma and PF following DP.

Conclusions

Additional suturing of the pancreatic stump in DP and use of a two-row stapler tended to be associated with a higher incidence of PF, but these were not risk factors. We suggest that the thickness of the pancreas may be an independent risk factor, and that PF could be reduced by using a stapler with a black cartridge with a reinforcing material for pancreatectomy for a pancreas of 14 mm or less in thickness and when the bleeding volume is below 750 mL.

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Author's contribution: M.T. designed the study; M.T., T.M., J.L., K.K., Y.M., and R.O. analyzed the data; Y.O. and K.F. supervised the experiments; M.T. and Y.O. wrote the manuscript.

Ethics statement: The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (M21297). Details about the study were disclosed in our website and the potential participants were given the opportunity to decline to be further enrolled in the study (optout).

Conflicts of interest: None declared.

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