

Clip on Staple Method Reduces Clinically Relevant Pancreatic Fistula After Distal Pancreatectomy

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Abstract. *Background/Aim:* In order to overcome postoperative pancreatic fistula (POPF) after distal pancreatectomy (DP), we have developed a new simple technique-Clip on Staple method. *Patients and Methods:* In Clip on Staple method, pancreatic parenchyma was divided using a stapling device with a stepped-height staple design to make linear compression line, and thereafter, the full length of the staple line was reinforced by multiple clips. Clinical outcomes were retrospectively compared between Clip on Staple group (n=23) and Non-Clip group (n=38). *Results:* The incidence of clinically relevant POPF (CR-POPF) was significantly lower in the Clip on Staple group than in the Non-Clip group (4.3 and 36.8%, $p=0.005$). Multivariate logistic regression analysis revealed that only Clip on Staple method was an independent predictive factor of a decrease in the occurrence of CR-POPF. *Conclusion:* The Clip on Staple method, a simple and easily applicable technique even in laparoscopic surgery, significantly reduced the occurrence of CR-POPF among patients undergoing DP.

Distal pancreatectomy (DP) is a common procedure for the treatment of benign or malignant pancreatic disease (1-3). Postoperative pancreatic fistula (POPF) is the leading cause of morbidity following DP, with a reported frequency of 5% to 60% (4, 5). It is associated with more severe life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage and sepsis (6-9). Furthermore, in case of malignancy, it has a negative impact on cancer recurrence and survival (10). Various strategies have recently been attempted to overcome such complication (5, 11-15). Although the stapler closure of the pancreatic stump became the standard technique that provides a steady quality of

closure for every surgeon, the multicenter randomized DISPACT trial failed to show the superiority of the stapler closure over the hand-sewn closure (16). Subsequently, several other techniques such as mesh reinforcement, fibrin glue sealant, or pancreaticojejunostomy for pancreatic stump have been reported with some favorable outcomes (13, 17-20). Despite vigorous efforts of surgeons to reduce the incidence of POPF, no simple and reliable technique has been established to overcome POPF to date.

Based on our hypothetical pathogenesis of pancreatic fistula, we thought that an ideal stump closure technique after DP should achieve both a linear compression line and tight and durable closure of the cutting line. Thus, we have introduced a new technique, which is composed of pancreas division using a stapling device with stepped-height staple design, in combination with further reinforcement of the staple line with multiple clips. In this report, we described the theoretical basis of the new technique, which was designated as the Clip on Staple method, and retrospectively analyzed its clinical outcome.

Patients and Methods

Patients. Between April 2014 and November 2018, 80 patients underwent DP in 2 participating hospitals. The pancreatic parenchymal transection method was selected according to the primary surgeon's preferences. Finally, a total of 61 patients who underwent DP using a linear stapler were enrolled in this study. Data on patients' demographics, clinicopathological features, operative information, incidence of complication, and postoperative course were collected from prospectively recorded patient's database and electronic medical records and analyzed retrospectively. Written informed consent was obtained from all patients preoperatively. The study protocol was approved by the Institutional Review Board in both hospitals (697 and 2018-8-4).

Clip on Staple method. Our hypothetical pathogenesis of pancreatic fistula after DP using a linear stapler is shown in Figure 1. First, when the staples are too thick compared to the pancreatic parenchyma, incomplete closure of the cutting line caused by loose compression could cause leakage from the main or branch pancreatic

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Key Words: Complication, pancreas, pancreatic fistula.

ducts in the stump. Second, when the staples are too thin, abrupt compression and narrowing of parenchyma may cause too much pressure on the edge of the cartridge, which could cause tear of the serosa or parenchyma. Third, when the staple line is sutured, the needle hole and stitch could cause a small laceration of the serosa. And forth, in case of thick pancreas, there would be some expanding force of compressed parenchyma at the part of the staple line. If this expanding force overwhelms the holding power of the staples, then “delayed loosening of the staples” may occur. Therefore, the ideal technique should achieve both linear compression and tight and endurable closure of the cutting line without suturing. Thus, we have introduced the “Clip on Staple method”. After dividing the pancreatic parenchyma using a linear stapler, the full length of the staple line was reinforced by multiple clips (Figure 2A). At this time, special attention was paid to apply the clips up to the 2nd of 3 staple lines in order to make the compression line linear as much as possible, and without affecting the thickness of the 3rd staple line (Figure 2B, C). For the same reason, the Endo-GIA™ Tri-Staple™ cartridge (Medtronic, Minneapolis, MN, USA) was used for the Clip on Staple method because it is equipped with a stepped-height staple design, which may reduce too much stress on the edge of the cartridge and help create a linear compression line. The pancreas was gently clamped by the cartridge and fired slowly, taking 3 min at a fixed speed, thereafter left for 2 min with the cartridge held shut and divided. As a clipping device, the DS Titanium Ligation Clip (B.Braun Aesculap®, Germany) (SM size, without latch) was used.

Perioperative management. At least one 19 Fr. J-Vac silicon drain was placed near the pancreatic stump. The amylase level of the drainage fluid was measured until the drain was removed. The drain was removed until postoperative day 8 if the drainage fluid was clear and pancreatic fistula and bacterial contamination were absent. Prophylactic octreotide was not administered in any cases of the current series. All patients were followed-up for 3 months after surgery or until discharge, whichever came last. The pancreatic fistula was classified as biochemical leak (BL) and grade B and C according to the International Study Group on Pancreatic Fistula (ISGPF) 2016. Grade B and C were defined as clinically relevant POPF (CR-POPF) (21).

Statistical analysis. Descriptive statistics were expressed as mean±standard error (SE) and compared using a two-tailed unpaired Student’s *t*-test. Categorical data were compared using the Chi-square test. A multivariate logistic regression was also used to identify demographic and clinical characteristics that could be independently predictive of CR-POPF. Statistical analyses were performed using the JMP 14 software (SAS Institute, Cary, NC, USA). A *p*-value <0.05 was considered as statistically significant.

Results

Patient characteristics. Among 61 patients who underwent DP with stapler closure for the pancreatic stump, the Clip on Staple method was applied on 23 patients (the Clip on Staple group). The other 38 patients were classified as the Non-Clip group. At the beginning of this study period, the Clip on Staple method was applied only in laparoscopic surgery. However, such method was applied since 2017 in

both laparoscopic and open surgeries. Table I shows the baseline patient characteristics in both groups. No significant difference was observed in the age, gender, body mass index (BMI), indication for surgery, and American Society of Anesthesiologists risk score between the two groups. Laparoscopic surgery was performed in 21 out of 23 patients (91%) of the Clip on Staple group and in 23 out of 38 patients (61%) of the Non-Clip group (*p*=0.017). Accordingly, the operative time was significantly longer in the Clip on Staple group than in the Non-Clip group (*p*=0.027). About two-thirds of the Non-Clip group used the Powered Echelon Flex® as a stapling device, and the other patients used the Endo-GIA™ Tri-Staple™ cartridge. Meanwhile, all patients in the Clip on Staple group used the Endo-GIA™ Tri-Staple™ cartridge (*p*<0.001). Suture reinforcement of the staple line was performed in 8 of 38 patients in the Non-Clip group. However, none of the patients in the Clip on Staple group required suture reinforcement. No significant difference was noted in the thickness of the pancreatic cutting line between both groups (12.9±0.7 and 11.9±0.6 mm, *p*=0.836).

Pancreatic fistula and postoperative complication. Table II shows the surgical outcomes of the two groups. Grade B POPF was observed among 14 patients (36.8%) in the Non-Clip group and in 1 patient (4.3%) in the Clip on Staple group. None of the patients in both groups had Grade C POPF. Accordingly, the incidence of CR-POPF was significantly lower in the Clip on Staple group than in the Non-Clip group (4.3% vs. 36.8%, *p*=0.005, Figure 3). The overall morbidity rate (any grade of the Clavien-Dindo classification) was 19 patients (50%) in the Non-Clip group and 9 patients (39%) in the Clip on Staple group. Among them, the incidence of severe complication (grade 3a or more) was significantly lower in the Clip on Staple group (zero patient) than that in the Non-Clip group (8 patients, 21.6%, *p*=0.019). In the Non-Clip group, there were 8 patients with intra-abdominal abscess, 5 with intra-abdominal hemorrhage, 5 with percutaneous or endoscopic drainage, and 1 with delayed gastric emptying. In contrast, none of the patients in the Clip on Staple group developed such complications. Only 1 patient in the Clip on Staple group developed CR-POPF, whose pancreas was 19-mm thick (Figure 4), and the drain was placed until the 27th postoperative day. The mean drain placement days and mean hospital stay were also significantly shorter in the Clip on Staple group than in the Non-Clip group. There was no reoperation or mortality within 90 days in both groups.

Predictive factors for the development of CR-POPF. To identify any predictive factors for the development of CR-POPF, univariate and multivariate analyses were performed (Table III). Univariate analysis implicated the BMI and

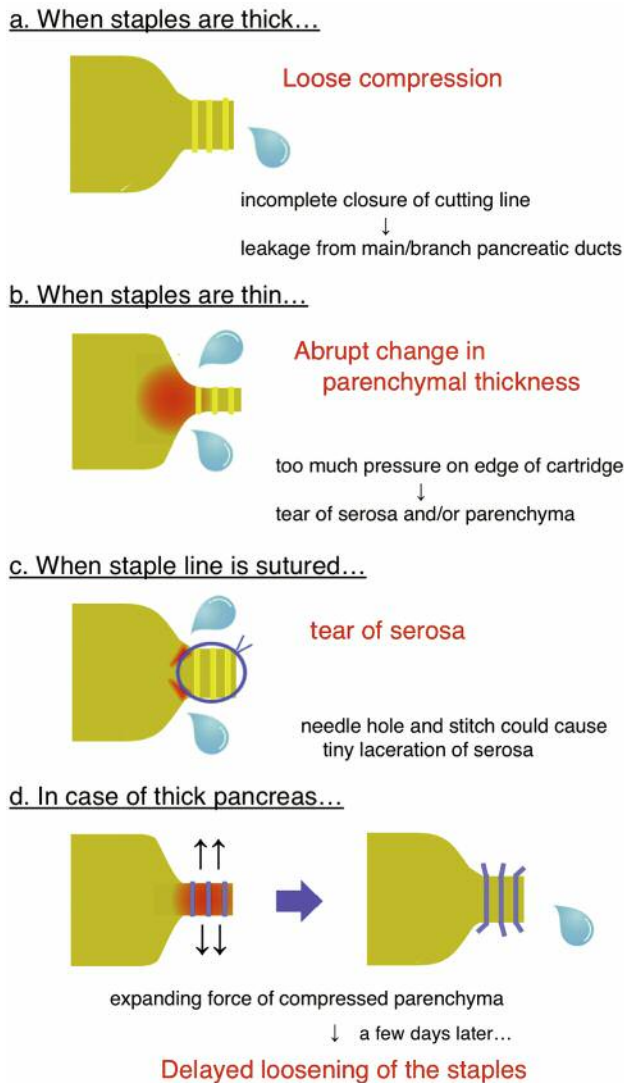


Figure 1. Hypothetical pathogenesis of pancreatic fistula after distal pancreatectomy using a stapling device. (a) When the staples are too thick, incomplete closure of the cutting line due to loose compression could cause leakage from the pancreatic ductules on the stump. (b) When the staples are too thin, abrupt compression and narrowing of the parenchyma may cause too much pressure on the edge of the cartridge, which could cause tearing of the serosa or parenchyma. (c) When the staple line is sutured, the needle hole and stitch could cause a small laceration of the serosa. (d) In case of thick pancreas, there would be some expanding force of compressed parenchyma at the part of the staple line. If this expanding force overwhelms the holding power of the staples, then “delayed loosening of staples” may occur.

application of the Clip on Staple method. In multivariate logistic regression analysis, application of the Clip on Staple method was the only variable that predicted a decrease in the occurrence rate of CR-POPF (odds ratio=0.08, 95% confidence interval=0.01-0.70, $p=0.022$).

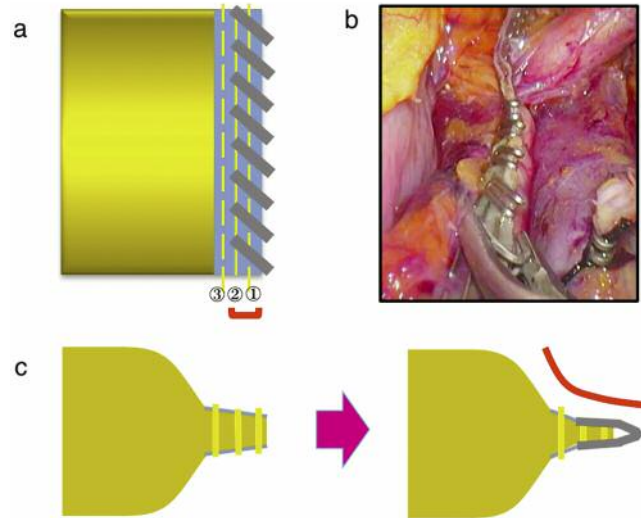


Figure 2. Schema of the technical aspects of the Clip on Staple method. (a, b) After dividing the pancreatic parenchyma using a stapling device, the full length of the staple line was reinforced by multiple clips. (c) Special attention was paid to apply clips up to the 2nd of 3 staple lines in order to make the compression line linear as much as possible, without affecting the thickness of the 3rd staple line.

Discussion

With the worldwide spread of the application of a minimally invasive approach for DP both in benign and malignant diseases, the use of a stapling device for pancreatic transection is becoming more popular (2, 22). Although its use seemed to offer nearly constant quality in terms of surgical outcomes regardless of the surgeon's experiences, the occurrence of POPF remained a significant clinical issue to be further refined (5, 16). We initially considered the theoretical basis for the occurrence of POPF following stapler closure to improve the quality of stapler closure of the pancreatic parenchyma. Based on the theoretical pathogenesis depicted in Figure 1, we have figured out two essential points to reduce the incidence of POPF after DP. The first point is the linear narrowing of the compression line of the pancreatic stump. Thinner staples would produce better results in achieving adequate closure of the pancreatic stump. However, thin staples cause abrupt narrowing of the pancreatic parenchyma, resulting in too much burden and possible tear of the compressed parenchyma (23). On the other hand, using too thick staples would cause loose stump compression, resulting in pancreatic juice leakage from the ductules in the stump. Therefore, concomitant use of relatively thick staples with stepped-height design, and additional clipping reinforcement on the edge of the stump would be the most ideal method in achieving both linear narrowing of the compression line as much as possible, and

Table I. Patient characteristics according to the groups.

	Non-Clip group (n=38)	Clip on Staple group (n=23)	p-Value
Preoperative status			
Age	68.9±1.7	72.1±2.1	0.238
Gender (Male/Female)	22/16	11/12	0.597
Body mass index (kg/m ²)	22.9±0.6	22.3±0.8	0.580
Indication for surgery			0.110
Pancreatic ductal adenocarcinoma	13	6	
Intraductal papillary mucinous neoplasms	15	9	
Mucinous cystic neoplasms	3	3	
Serous cystic neoplasms	2	0	
Neuroendocrine tumor	3	0	
Other disease	2	5	
Malignant tumor	21 (55.3%)	9 (39.1%)	0.293
ASA (1/2/3)	0/30/7	0/21/2	0.460
Operative characteristics			
Surgical approach			0.017
Open	15	2	
Laparoscopic	23	21	
Procedure			0.341
DP with splenectomy	20	9	
Splenic vessel preserving DP	7	8	
RAMPS	11	6	
DP-CAR	1	0	
Pancreatic texture			0.522
Soft	36	23	
Hard	2	0	
Stapler			<0.001
Endo-GIA™ Tri-Staple™	12	23	
(Reinforced Reload)	2	15	
Powered Echelon Flex®	26	0	
Thickness of the staples			0.154
Thin (camel)	2	0	
Medium (purple or green)	26	12	
Thick (black)	10	11	
Suture reinforcement of staple line	8	0	
Thickness of the pancreas (mm)	11.9±0.6	12.9±0.7	0.836
Operative time (min) median (IQR)	311 (183-385)	375 (313-419)	0.027
Blood loss (ml) median (IQR)	260 (95-980)	100 (0-310)	0.007
Blood transfusion	5	0	0.147

Values are expressed as mean±standard error unless otherwise indicated. ASA: American Society of Anesthesiologists' risk class; DP: distal pancreatectomy; RAMPS: radical antegrade modular pancreatectomy; DP-CAR: distal pancreatectomy with celiac axis resection; IQR: interquartile range.

steady closure of the pancreatic ductules in the stump. Although the use of the Endo-GIA™ Tri-Staple™ cartridges revealed no statistical superiority (Table III), possibly due to the small sample size, we believe that the stepped-height staple design, which helps in the gradual narrowing of the compression line, might have contributed to some extent in reducing the occurrence of POPF. The second point to reduce the incidence of POPF is a firm and endurable closure of the stump. We believe that reinforcement of the staples is necessary not only for securing the closure of pancreatic

ductules on the stump after using relatively thick staples, but also for avoiding possible “delayed loosening of the staples” caused by the expanding force of the compressed pancreatic parenchyma after surgery. In a clinical setting, we sometimes experience the delayed occurrence of POPF despite initial good clinical course following stapler closure. We speculated that such cases might be attributed to delayed loosening of the staples with time. Another possible example is that, in case of CR-POPF with intra-abdominal abscess formation, we sometimes observe direct communication between the

Table II. *Postoperative outcomes according to the groups.*

	Non-Clip group (n=38)	Clip on Staple group (n=23)	<i>p</i> -Value
Pancreatic fistula*			
Biochemical leak	12 (31.6%)	12 (52.2%)	
Grade B POPF	14 (36.8%)	1 (4.3%)	
Grade C POPF	0	0	
CR-POPF	14 (36.8%)	1 (4.3%)	0.005
Amylase level of drainage fluid on POD3 (IU/l) median (IQR)	432 (139-2226)	553 (137-2004)	0.950
Complication			
Clavien-Dindo classification (1/2/3a/3b/4/5)	5/6/8/0/0/0	7/2/0/0/0/0	0.046
Severe complication (3a or more)	8 (21.6%)	0	0.019
Intra-abdominal abscess	5 (13.1%)	0	0.147
Intra-abdominal hemorrhage	1 (2.6%)	0	1.000
Persistent drainage over 3 weeks	13 (34.2%)	1 (4.3%)	0.010
Percutaneous or Endoscopic drainage	5 (13.1%)	0	0.147
Delayed gastric emptying (any grade)	1 (2.7%)	0	1.000
Drain removal (days) mean±SE (median)	17.4±2.7 (7)	9.6±3.5 (7)	0.041
Hospital stay (days) mean±SE (median)	27.5±3.7 (15)	14.9±4.8 (13)	0.021
Re-operation within 90 days	0	0	
Mortality within 90 days	0	0	

*Pancreatic fistula is defined according to International Study Group of Pancreatic Fistula (ISGPF) 2016. POPF: Postoperative pancreatic fistula; CR-POPF: clinically relevant postoperative pancreatic fistula; POD: postoperative day; IQR: interquartile range; SE: standard error.

Table III. *Analyses of predictive factors for the development of CR-POPF.*

	Univariate analysis			Multivariate analysis		
	OR	95%CI	<i>p</i> -Value	OR	95%CI	<i>p</i> -Value
Age	0.95	0.90-1.01	0.075	0.95	0.89-1.02	0.162
Body mass index (kg/m ²)	1.18	0.99-1.40	0.049	1.2	0.97-1.47	0.063
Laparoscopic vs. Open	0.47	0.14-1.62	0.233			
Male vs. Female	0.96	0.30-3.09	0.945			
Diabetes melitus	1.56	0.32-7.52	0.588			
Malignant vs. Benign	0.73	0.22-2.38	0.596			
Thickness of the pancreas cutting line (mm)	1.08	0.91-1.27	0.399			
Powered Echelon Flex® vs. Endo-GIA™ tri-staple	1.78	0.55-5.75	0.337			
Reinforced cartridge vs. other cartridge	0.32	0.06-1.59	0.163			
Clip on Staple vs. Non-Clip	0.08	0.01-0.64	0.018	0.08	0.01-0.70	0.022

CR-POPF: Clinically relevant postoperative pancreatic fistula; OR: odds ratio; CI: confidence interval.

main pancreatic duct and abscess cavity beside the pancreatic stump. We speculated that such communication might be a result of delayed loosening of the staples. Communication with the main pancreatic duct could result in enteric bacterial contamination, and subsequent activation of pancreatic enzymes would cause deterioration of biochemical leakage into CR-POPF. In the current study, biochemical leakage in the Clip on Staple group was 52%, but CR-POPF was just

4%. Clip on Staple method might have reduced the occurrence of CR-POPF, at least in part, by avoiding “delayed loosening of the staples”. Although some previous reports showed the effectiveness of combined stapler and suture closure, a meta-analysis by Zhang *et al.* failed to show the superiority of the combined closure over the stapler closure alone (4, 11). Because the needle hole and stitch can possibly cause a small laceration of the serosa, reinforcement

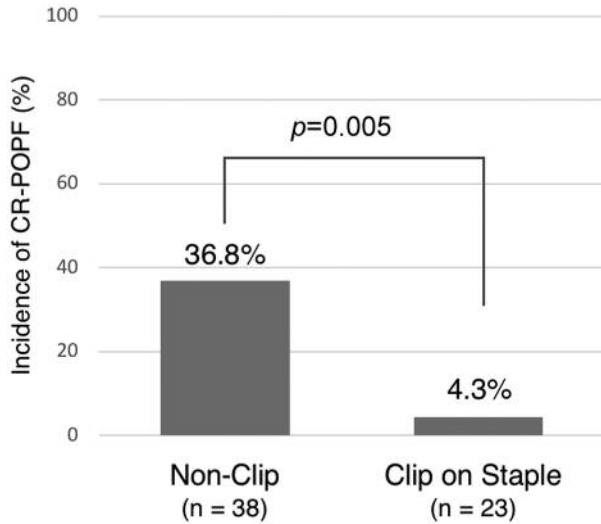


Figure 3. Comparison of the incidence of clinically relevant postoperative pancreatic fistula (CR-POPF) after distal pancreatectomy between the two groups. The incidence of CR-POPF was significantly lower in the Clip on Staple group than in the Non-Clip group (4.3% vs. 36.8%, $p=0.005$).

by clipping on the staples, but not suturing, would be a better measure to ensure a steady and enduring closure.

The current study revealed the effectiveness of the Clip on Staple method in preventing CR-POPF. Previous attempts in an effort to reduce POPF after DP include the trial reported by Hamilton *et al.* demonstrating an excellent result by using mesh reinforcement of a pancreatic transection line, resulting in 1.9% of ISGPF grade B and C leaks (13). Although the extremely low incidence rate cannot be deemed as an actual effect of mesh reinforcement, because cases with too thick pancreas were excluded from the study, we think that using mesh buttress cartridges might decrease the risk of sharp staples cutting into the pancreatic parenchyma, resulting in a tear. Therefore, currently we utilize mesh-reinforced cartridges with the Clip on Staple method, although its clinical effectiveness was not demonstrated in the current study (Table III). Another interesting trial is the report by Kawai *et al.*, which evaluated the effect of pancreaticojejunostomy *versus* stapler closure after DP (20). Although the trial could not demonstrate the superiority of pancreaticojejunostomy over stapling closure, the subgroup analysis suggested the potential effect of such procedure in patients with a thick pancreas. However, applying pancreaticojejunostomy in laparoscopic DP is quite difficult and time-consuming. One of the merits of the Clip on Staple method is that it is a simple technique; thus, it is easily applicable even in laparoscopic surgery.

There were several limitations in our study. The mean thickness of the pancreas was around 12 mm, with a maximum thickness of 20 mm. Therefore, the effectiveness of the Clip on Staple method in too thick pancreas, over 20 mm, could not be

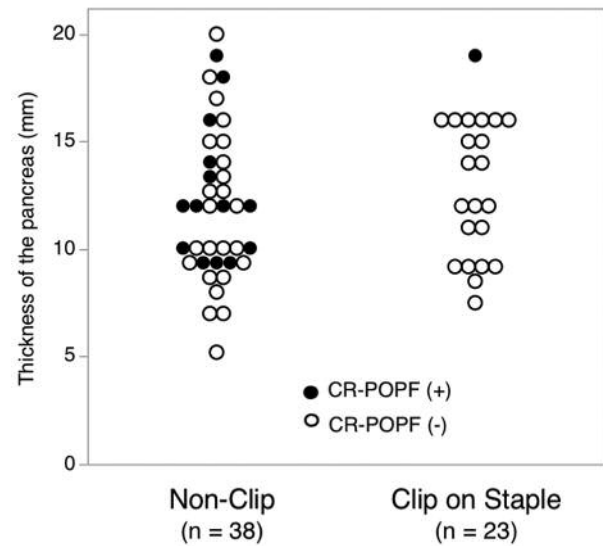


Figure 4. Relationship between the thickness of the pancreas and the occurrence of clinically relevant postoperative pancreatic fistula (CR-POPF). In the Non-Clip group, CR-POPF occurred among 14 patients, where the thickness of the pancreas was 9 mm or greater. Meanwhile, only 1 patient in the Clip on Staple group experienced CR-POPF, wherein the thickness of the pancreas was 19 mm. The black circle represents the patient with CR-POPF, and the white circle denotes patients without CR-POPF.

confirmed. In general, the safe application of the stapling device is difficult for a too thick and firm pancreas because too much compression in such condition causes tearing of the serosa and parenchyma (23, 24). Therefore, in case of too thick pancreas in which even a stapling device cannot be applicable, other techniques, such as pancreaticojejunostomy, should be considered instead of the Clip on Staple method. Another limitation is that this is a retrospective study, and only 1 (first author) among 3 participating primary surgeons performed the Clip on Staple method. Although the perioperative management was almost similar, minor differences due to the surgeon's preferences might have affected the surgical outcomes. Additional subgroup analysis using patients treated by the first author was performed to eliminate this possibility. Consequently, the effectiveness of the Clip on Staple method was reconfirmed (data not shown).

In conclusion, the Clip on Staple method, which is composed of pancreas division using stapling device with stepped-height staple design, in combination with further reinforcement of the staple line with multiple clips, was a simple and easily applicable technique even in laparoscopic surgery. It significantly reduced the occurrence of CR-POPF and associated complications among patients undergoing DP. A randomized controlled trial is needed to further clarify the usefulness of this technique.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Study concepts, M.N.; Study design, M.N., H.U., T.N.; Data acquisition, T.T., R.M., T.M.; Data analysis, M.N., H.U.; Drafting the manuscript, M.N.; Critical revision of the manuscript, T.T., R.M., T.M., H.U., T.N.; Final approval of the manuscript, M.N., T.T., R.M., T.M., H.U., T.N.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Received October 16, 2019

Revised October 29, 2019

Accepted October 30, 2019