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Effect of the use of reinforced stapling on the occurrence of pancreatic fistula after distal pancreatectomy: results of the REPLAY multicenter randomized clinical trial

REPLAY: REinforcement of the Pancreas in distal pAncreatectomy

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Reinforced stapling in pancreatectomy

Objective: The aim of the study was to evaluate the impact of the use of a reinforced stapler (RS) during distal pancreatectomy on postoperative outcomes.

Background: Distal pancreatectomy (DP) remains associated with significant postoperative morbidity owing to pancreatic fistula (PF). To date, there is no consensus on the management of the pancreatic stump. The use of an RS potentially represents a simple way to decrease the rate of PF.

Methods: The REPLAY study (NCT03030170) is a prospective, multicenter, randomized study. Patients who underwent DP were randomized (1:1 ratio) in 2 groups for the use of a standard stapler (SS) or an RS to close remnant pancreatic parenchyma. The primary endpoint was the rate of overall PF. Secondary endpoints included severity of PF, length of hospital stay, overall morbidity and rate of readmission for a PF within 90 days. Participants were blinded to the procedure actually carried out.

Results: A total of 199 were analyzed (SS n = 99, RS n = 100). One patient who did not undergo surgery was excluded. Baseline characteristics were comparable in both groups. The rate of overall PF was higher in RS group (SS 67.7%, RS 83%, $P = 0.0121$) but the rate of clinically relevant PF was similar (SS: 11.1%, RS: 14%, $P = 0.5387$). Mean length of total hospital stay, readmission for PF, postoperative morbidity and mortality at 90 days were similar.

Conclusion: The results of this randomized clinical trial did not favor the use of RS during DP to reduce the rate of PF.

Despite the reduction in morbidity and mortality over the past 20 years, particularly at high-volume centers, pancreatic surgery is still associated with significant postoperative morbidity in up to 60% of the cases.^{1,2} In the case of distal pancreatectomy (DP), the main complication remains the occurrence of a postoperative pancreatic fistula (PF) in 30% to 50% of the cases.² This complication can lead to an increased risk of hemorrhage, delayed gastric emptying and prolongation of the length of hospital stay.³ The main risk factor for PF after PD is a thick and fatty pancreatic parenchyma.^{4,5} A recent retrospective analysis of 2,026 DP from the international multi-institutional distal pancreatectomy study group also highlighted young age, obesity, neuroendocrine and nonmalignant pathologies as PF risk factors.⁶ Given these unchangeable factors, one of the priorities in pancreatic surgery is to therefore find a new way to decrease the occurrence of PF. Currently, there is no optimal technique recommended for closure of the distal stump during DP.⁷ Some recommendations from the International Study Group of Pancreatic Surgery (ISGPS) have strong support. Manual closure by elective suture of the pancreatic duct or stapling produces similar outcomes.^{8,9} Reinforcement of stump closure with absorbable fibrin collagen sealant sponge was not associated with a significant decrease in the occurrence of PF in several randomized clinical studies and is not recommended in the last Cochrane Review.^{1,10-13}

The use of a staple reinforcement is potentially a simple way to reduce the development of PF. In 2012, Hamilton et al. reported a reduction in the incidence of clinically significant PF in a single institution randomized controlled trial. However, each group included only 50 patients and the type of reinforcement was not randomized which led to a weak level of agreement in ISGS guidelines.¹⁴

The aim of this study was to compare the impact of the use of a simple stapler loader with that of a polyglycol acid reinforced stapler loader for closure of the pancreatic parenchyma on the postoperative outcomes of DP.

METHODS

Design and Patients

The REPLAY study (NCT03030170) is a prospective, national, multicenter, randomized, superiority, open-label and parallel group trial. The French National Agency for Medicine and Health Product Safety approved the study. Patients were enrolled in 7 French centers. Adult patients with an indication of DP for any benign or malignant pancreatic lesion located in the body or the tail of the pancreas were eligible for randomization. All patients provided written consent before randomization. Patients with histories of pancreatic abdominal surgery, severe comorbidity (renal failure requiring hemodialysis, major respiratory failure, heart failure \geq NYHA stage 3), subjected to legal protection or deprived of liberty, pregnant or participating or who intended to participate in another clinical study making follow-up impossible were not included. Enrolled patients who were subsequently unable to undergo surgery were excluded. The level of section of the pancreatic parenchyma was chosen by the surgeon according to the location and type of tumor. Drain placement and postoperative use of somatostatin analogs were left to the discretion of the surgeon. The trial was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Guidelines.¹⁵ A Clinical Research Assistant (CRA) mandated by the sponsor (CHU Rennes) ensured the successful completion of the study, the collection of the data, their documentation, registration and reporting during quality control visits in accordance with the Standard Operating Procedures set up within the CHU de Rennes and in accordance with Good Clinical Practice and the legal and regulatory provisions in force. An independent Data Safety Monitoring Board (DSMB) determined whether the trial continued to be ethically and scientifically justified over time. An interim analysis after enrollment of half of the patients was performed.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio of DP with standard stapling (SS) of the pancreas using "Endo GIA Articulating X-tra Thick reload with Tri-Staple Technology" (black cartridge) vs DP with

polyglycol acid reinforced stapling (RS) using "Endo GIA Articulating Reinforced Reload with Tri-Staple Technology". Randomization was done on the day of surgery in the operating room. Although blinding in the operating room was not possible, participants were not informed after their surgery of the procedure actually carried out.

Patients were assigned to the randomization group in chronological order of randomization numbers using a centralized randomization method via the Ennov software (Ennov Clinical®, Groupe Ennov, Paris, France). A notification was sent to the investigator indicating the patient's inclusion number, the randomization number and the randomization group (SS or RS). The randomization list was stratified by center. It was developed by a computer program that generated blocks of varying sizes (here 4 and 6 numbers). The order of block sizes and the order of randomization groups in each block were randomly generated.

Study Endpoints

The primary endpoint was the rate of overall postoperative PF defined by the International Study Group of Pancreatic Fistula (ISGPF) criteria within 90 days: increased amylase level in the drainage fluid that is 3 times higher than the blood amylase on postoperative day (POD) 3 or POD 5 (if available), or postoperative discovery of a collection in contact with the pancreatic opening on an abdominal computed tomography ¹⁶. As PF classification changed after study protocol deposit, data recording about PF was done using the new classification ¹⁷. Postoperative computed tomography scan was performed only in case of a clinical or biological focal point (fever, unusual pain, biological inflammatory syndrome).

The secondary endpoints were length of hospital stay, severity of PF according to the ISGPF classification (biochemical leak and clinically relevant PF), occurrence of delayed gastric emptying (DGE) and its severity according to International Study Group of Pancreatic Surgery (ISGPS) criteria, occurrence of a postoperative hemorrhage (PPH) and its severity according to ISGPS criteria, overall morbidity classified according to the Clavien-Dindo Classification, rate of readmission for a PF and postoperative mortality within 90 days.¹⁷⁻²⁰

Data were compiled in an electronic data collection form. Monitoring of the data was performed at each study site by a clinical research technician in charge of the protocol.

Sample Size Estimation and Statistical Analysis

The risk of developing PF was considered to be 50% after DP. Assuming a 20% decrease in the risk of a PF by reinforcing the stapling line, with a risk α set at 0.05 and a study power at 80% (bilateral test), the number of subjects required per arm was 96 (a study population of 192 patients). To account for possible patients who could not be assessed, we increased the total patient sample size to 200 patients (100 patients in each arm). This was an intention-to-treat study, i.e., all randomized and assessed patients were analyzed in their treatment arm attributed to them by randomization.

Qualitative data are presented as number and percentage and quantitative data are presented as median and interquartile range (IQR) or mean and standard deviation (SD), as appropriate. The normality of the distribution of the quantitative variables was verified. Student's *t*-test or the Mann-Whitney test, as appropriate, were used to compare the quantitative variables and the Chi² test or Fisher's exact test, as appropriate, were used to compare the qualitative variables between groups. An interim analysis after inclusion of half of the patients and a final analysis were performed. The research discontinuation criterion was the alpha risk spending function with the O'Brien-Fleming boundaries. The cumulative values of alpha for each analysis were: 0.00305 for the first analysis, and 0.04900 for the final analysis (nTerim, V4.0, Statistical solutions Ltd, Cork, Ireland). Missing data were not replaced. Statistical analyses were performed using SAS software v9.4 (SAS Institute, Cary, NC, USA).

Source of Funding

The trial was funded by Covidien/Medtronic. The funder had no role in collection, management, analysis, and interpretation of data, writing of the report or the decision to submit the report for publication.

RESULTS

Between August 2017 and April 2021, 207 patients were screened for eligibility. Two hundred patients were randomized of whom one did not undergo surgery owing to peritoneal carcinomatosis. DP was performed with SS for 99 patients and with RS for 100 patients (Fig. 1). Baseline characteristics were comparable for both groups (Table 1).

Intraoperative data are shown in Table 2. Type of surgical approach was similar with a majority of laparoscopies in both groups (72.4%). The rates of conversion were similar (6.1% with SS, 10.0% with RS, $P = 0.31$). Stapling of the pancreas was feasible in 99% of the patients (98% with SS, 100% with RS, $P = 0.25$). Splenectomy was associated for an average of one third of the patients (35.4% in SS group, 37% in RS group, $P = 0.81$). Pancreatic texture was soft in a majority of patients (84.4% in SS group, 82.7% in RS group, $P = 0.85$). Operative time, blood loss and transfusion rate were similar in both groups.

Postoperative outcomes are shown in Table 3. There was no significant difference in the rate of clinically relevant PF between the groups ($P = 0.54$). The rate of overall PF (including biochemical leak and clinically relevant PF) was significantly higher in the RS group than in the SS group (83% vs 67.7%, $P = 0.01$) with a tendency of more biochemical leak in the RS group ($P = 0.0696$). The rates of DGE and PPH were similar. A peripancreatic collection was diagnosed in 46 patients, either at initial hospitalization or at readmission, with no significant difference between the two groups. Not all peripancreatic collection were related to a clinically relevant PF and, if not, were considered associated with a biochemical leak.

The Clavien–Dindo \geq III complication rate was not different between the groups (9.1% in the SS group vs 15% in the RS group, $P = 0.20$). One death occurred in the SS group. Length of hospital stay was 8.0 [7.0–11.0] days in the SS group and 8.0 [6.0–11.0] days in the RS group ($P = 0.85$). Readmission for PF occurred for 8 patients in the SS group (8.1%) vs 8 patients in the RS group (8.0%) ($P = 0.98$). Other reasons for readmission were hemorrhage (n=5), thrombosis of mesenteric or portal vein (n=4), pain (n=3), sepsis (n=3), DGE (n=2), acute pancreatitis (n=2), digestive perforation (n=2), chylous fistula

(n=1), decompensated diabetes (n=1), digestive occlusion (n=1), post-chemotherapy *Clostridium* infection (n=1), nephrectomy (n=1), vertebral fracture (n=1), cerebral ischemic stroke (n=1), transurethral resection of the prostate (n=1), costal fracture (n=1), acute urinary retention (n=1), pyelonephritis (n=1), hip prosthesis infection (n=1) and implanted port infection (n=1). Some patients were readmitted for multiple reasons (PF and/or hemorrhage and/or DGE).

DISCUSSION

This prospective multicenter randomized trial failed to show a benefit of RS for closure of pancreatic stump to reduce the rate of PF after DP. Moreover, the rate of overall PF was higher in the RS group but without clinically relevant impact. No differences were observed in the rates of DGE, hemorrhage or length of hospital stay.

With 199 patients, this is the largest trial confirming the lack of benefit of RS in DP. The HiSCO-07 trial randomized 122 patients to receive bare or polyglycol acid reinforced stapler.²¹ No difference was shown in the rate of clinically relevant PF between the two groups except in a subset of patients with a pancreas transection thickness of <14mm. Recently, Wennerblom et al. published the results of a randomized controlled trial comparing SS and RS with an extracellular matrix biomaterial derived from submucosal tissue from pig small intestine.²² The trial also failed to demonstrate the expected reduction in PF rate. One of the limitations was the absence of recommendation for the type of stapler cartridge to be used.

In a recent retrospective study, Kang et al. noted that thickness was the strongest risk factor in predicting PF and proposed to adapt the type of cartridge to the thickness of pancreatic parenchyma.²³ In 2021, the results of a randomized controlled trial published by Landoni et al. showed no difference between bare stapled and ultrasonic transection of pancreatic parenchyma on PF rates after DP, contradicting the results of their previous retrospective study published in 2019.^{24,25} However, patients with a parenchymal thickness >17mm were excluded to avoid closure failure or parenchymal crushing after stapling.²⁵ In the present study, the technique was simple and reproducible using only one type of cartridge for thick tissue which made stapling feasible in 99% of the patients.

As noted in the latest ISGPS guidelines, management of the pancreatic wall is still lacking consensus owing to the poor level of agreement on technical topics.⁷ In 2017, a randomized clinical trial by Jang et al. showed that wrapping the stapled pancreatic stump with polyglycolic acid mesh decreases the rate of clinically relevant PF.²⁶ However, the use of fibrin glue associated with the mesh, the manual wrapping of the mesh and the choice of the type of cartridge left to the surgeon were

possible limitations to the study. A recent network meta-analysis highlighted reinforcement with round ligament or seromuscular patch after stapler or suture closure as potential ways to decrease PF.²⁷ All of those techniques should be explored in well-conducted randomized trials.

The mean rate of clinically relevant PF was 12.6% which is low compared with those reported in the literature from 15% to 40%.^{6,28} One could assume that the systematic use of a cartridge for thick tissue is responsible for this low rate. It also makes it more difficult to show a significative difference between the two groups.

In the present trial, laparoscopic approach was the principal surgical approach as opposed to an all-inclusive French national observational study published in 2015 with a majority of open approaches.²⁹ The recent trial published by Wennerblom et al. also presented a high rate of open approach (approximately 80%) probably owing to the period of inclusion between 2014 and 2016 before our trial. Since the LEOPARD trial recently demonstrated a shorter time to functional recovery, the laparoscopic approach has now become the standard approach for DP in high volume centers such as those in this trial.²⁸

The present trial has some limitations. First, sample size calculation was made before changes in PF definition according to the ISGPF classification. A calculation based only on reduction of the clinically relevant PF would be more appropriate. Second, only data in the texture of pancreas were collected but not on the thickness of pancreas. Studies highlighting thickness as a PF risk factor were published after the beginning of our study. A majority of soft pancreatic texture in our study avoided statistical analysis in the subgroups.

CONCLUSION

The current trial found no benefit on the rate of PF after the use of a reinforced stapling to transect pancreatic parenchyma during DP.

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FIGURE LEGEND

Figure 1: Flow chart.

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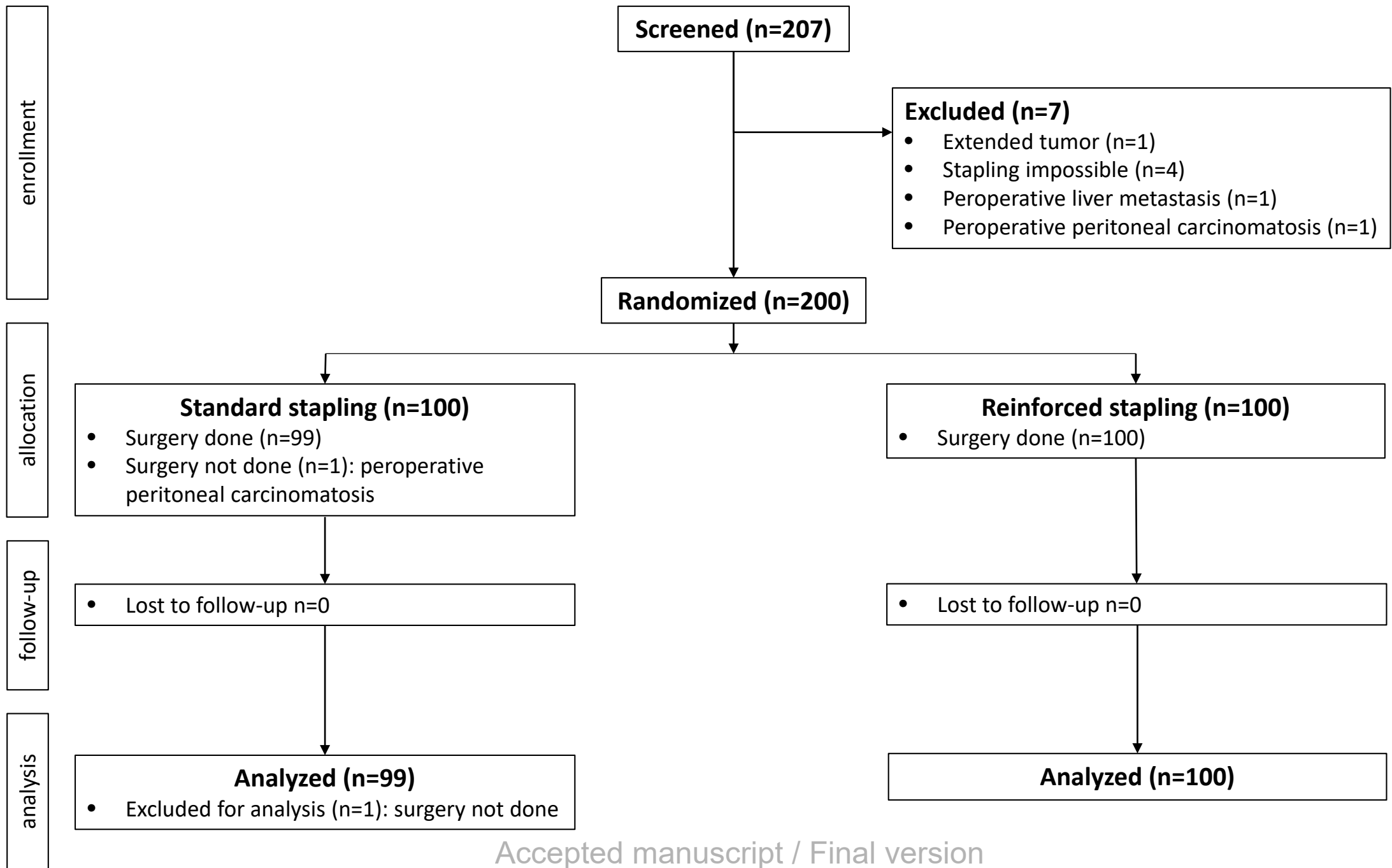


Table 1: Baseline characteristics

	Total (n=199)	Standard stapling (n=99)	Reinforced stapling (n=100)	P
Age, years	61.8 ± 13.5	62.5 ± 13.0	61.2 ± 14.0	0.51
Sex				0.18
Male	101 (50.8%)	55 (55.6%)	46 (46.0%)	
Female	98 (49.2%)	44 (44.4%)	54 (54.0%)	
Body mass index, kg/m ²	25.2 ± 4.7	25.3 ± 4.5	25.2 ± 4.9	0.88
Weight loss	36 (18.8%)	16 (16.8%)	20 (20.6%)	0.50
Current smoker	71 (35.7%)	33 (33.3%)	38 (38.0%)	0.49
ASA score				0.82
1	40 (20.2%)	21 (21.4%)	19 (19.0%)	
2	133 (67.2%)	66 (67.3%)	67 (67.0%)	
3	25 (12.6%)	11 (11.2%)	14 (14.0%)	
Chronic pancreatitis	5 (2.5%)	2 (2.0%)	3 (3.0%)	1.00
Diabetes mellitus	46 (23.1%)	21 (21.2%)	25 (25.0%)	0.53
Comorbidity				
Cardiovascular disease	97 (53.6%)	49 (53.3%)	48 (53.9%)	0.93
Lung disease	40 (22.1%)	23 (25.0%)	17 (19.1%)	0.34
Neurological disease	21 (11.6%)	10 (10.9%)	11 (12.4%)	0.75
Histology of malignant disease				0.34
Pancreatic adenocarcinoma	63 (41.7%)	36 (44.4%)	27 (38.6%)	
Endocrine tumor	46 (30.5%)	26 (32.1%)	20 (28.6%)	
Pseudopapillar and solid pancreatic tumor	5 (3.3%)	2 (2.5%)	3 (4.3%)	
Pancreatic metastasis of renal cancer	8 (5.3%)	4 (4.9%)	4 (5.7%)	
Malignant intrapapillar and mucinous neoplasm	17 (11.3%)	5 (6.2%)	12 (17.1%)	
Other	12 (7.9%)	8 (9.9%)	4 (5.7%)	
Neoadjuvant treatment	33 (16.6%)	17 (17.2%)	16 (16.0%)	0.82
Type of neoadjuvant treatment				0.66
Chemotherapy	27 (81.8%)	13 (76.5%)	14 (87.5%)	
Radiochemotherapy	6 (18.2%)	4 (23.5%)	2 (12.5%)	

Qualitative variables are expressed as number (%) and analyzed with χ^2 test or Fisher test.

Quantitative variables are expressed as means with standard deviations and analyzed with Student's *t*-test.

ASA = American Society of Anesthesiologists

Table 2: Surgical data

	Total (n=199)	Standard stapling (n=99)	Reinforced stapling (n=100)	P
Surgical time (min)	180.0 [140.0-240.0]	175.0 [141.0-240.0]	180.0 [140.0-245.0]	0.72
Surgical approach				0.57
Laparoscopy	144 (72.4%)	74 (74.7%)	70 (70.0%)	
Open	39 (19.6%)	19 (19.2%)	20 (20.0%)	
Conversion	16 (8.0%)	6 (6.1%)	10 (10.0%)	
Splenectomy	72 (36.2%)	35 (35.4%)	37 (37.0%)	0.81
Other organ resection	58 (29.1%)	25 (25.3%)	33 (33.0%)	0.23
Transverse or left colectomy	3 (5.2%)	1 (4.0%)	2 (6.1%)	0.08
Gastrectomy	7 (12.1%)	2 (8.0%)	5 (15.2%)	
Left adrenalectomy	17 (29.3%)	4 (16.0%)	13 (39.4%)	
Left nephrectomy	1 (1.7%)	0 (0.0%)	1 (3.0%)	
Other	30 (51.7%)	18 (72.0%)	12 (36.4%)	
Pancreatic texture				0.84
Soft	162 (83.5%)	81 (84.4%)	81 (82.7%)	
Firm	32 (16.5%)	15 (15.6%)	17 (17.3%)	
Feasibility of pancreatic stapling	197 (99.0%)	97 (98.0%)	100 (100.0%)	0.25
Problem during stapling procedure	12 (6.0%)	5 (5.1%)	7 (7.0%)	0.56
Need to perform hemostasis of pancreatic stump after stapling	40 (20.1%)	24 (24.2%)	16 (16.0%)	0.15
Transfusion	7 (3.5%)	3 (3.0%)	4 (4.0%)	1.00
Blood loss, mL	150.0 [80.0-300.0]	150.0 [80.0-300.0]	150.0 [100.0-300.0]	0.84

Qualitative variables are expressed as number (%) and analyzed with χ^2 test (K) or Fisher test (F). Quantitative variables are expressed as medians with interquartile ranges and analyzed with Mann-Whitney - Wilcoxon test.

Table 3: Postoperative outcomes

	Total (n=199)	Standard stapling (n=99)	Reinforced stapling (n=100)	P
Pancreatic fistula	150 (75.4%)	67 (67.7%)	83 (83.0%)	0.01
Biochemical leak	125 (62.8%)	56 (56.6%)	69 (69%)	0.07
Clinically relevant PF (grade B or C)	25 (12.6%)	11 (11.1%)	14 (14.0%)	0.54
Delayed gastric emptying	15 (7.5%)	9 (9.1%)	6 (6.0%)	0.41
Severity of DGE				1.00
Grade A	12 (80.0%)	7 (77.8%)	5 (83.3%)	
Grade B	3 (20.0%)	2 (22.2%)	1 (16.7%)	
Grade C	0 (0%)	0 (0%)	0(0%)	
Postoperative hemorrhage	8 (4.0%)	5 (5.1%)	3 (3.0%)	0.50
Severity of PPH				1.00
Grade A	2 (25.0%)	1 (20.0%)	1 (33.3%)	
Grade B	3 (37.5%)	2 (40.0%)	1 (33.3%)	
Grade C	3 (37.5%)	2 (40.0%)	1 (33.3%)	
Peripancreatic collection	46 (23.1%)	20 (20.2%)	26 (26%)	0.51
Radiologic drainage for peripancreatic collection	5 (2,5%)	2 (2%)	3 (3%)	1
Clavien-Dindo modified				0.20
Grade <III	175 (87.9%)	90 (90.9%)	85 (85.0%)	
Grade ≥III (severe)	24 (12.1%)	9 (9.1%)	15 (15.0%)	
Length of initial hospital stay, days	8.0 [7.0-11.0]	8.0 [7.0-11.0]	8.0 [6.0-11.0]	0.85
Length of total hospital stay (initial and readmission), days	9.0 [7.0-13.0]	8.0 [7.0-12.0]	9.0 [7.0-15.0]	0.21
Overall readmission	40 (20,1%)	19 (19,2%)	21 (21%)	0,75
Readmission for PF	16 (8.0%)	8 (8.1%)	8 (8.0%)	0.98

Qualitative variables are expressed as number (%) and analyzed with χ^2 test or Fisher test.

Quantitative variables are expressed as medians with interquartile ranges and analyzed with Mann-Whitney - Wilcoxon test

DGE = Delayed gastric emptying

PPH = Postoperative hemorrhage

PF = Pancreatic Fistula