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# The safety and efficacy of stapler method for transection of the pancreatic parenchyma during pancreatoduodenectomy (STRAP-PD trial): study protocol for a randomized control trial

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## Abstract

**Background** Pancreaticoduodenectomy is a highly difficult and invasive type of gastrointestinal surgery. Prevention of postoperative pancreatic fistula is important, and this may be possible by the stapler method.

**Methods** STRAP-PD is a single center randomized controlled trial. We compare a method of transecting the pancreatic parenchyma in pancreaticoduodenectomy using a surgical stapler device with a conventional transecting method using energy devices (e.g., scalpel, ultrasonic coagulator and incision devices). Patients with soft pancreas who are scheduled to undergo pancreaticoduodenectomy are randomized to arm A (conventional method) or arm B (stapler method). We aim to examine the safety and usefulness of dissection by the automatic suture device, with attention to the rate of pancreatic fistula ISGPF grade B or C and to postoperative complications. This is a single-center randomized study, which began in September 2023 at Wakayama Medical University Hospital.

**Discussion** Pancreatic parenchymal transection is typically performed either by direct incision using a scalpel or by employing energy devices such as ultrasonic coagulating cutting devices during pancreaticoduodenectomy. In a prospective pilot study, we conducted pancreatic parenchymal transection in 20 consecutive normal pancreatic cases during pancreaticoduodenectomy, observing postoperative pancreatic fistula grade B in one case (5%). Traditional methods involving scalpel incision or the use of ultrasonic coagulating cutting devices have been historically favored but perceived as technically challenging, and they have been reliant upon the surgeon's skill. Notably, relatively high incidences of postoperative pancreatic fistula among patients with soft pancreas have also been observed. Our proposed stapler method may therefore be a useful method responsible for reducing the development of pancreatic fistula. This method would be as part of minimally-invasive surgery for pancreaticoduodenectomy. It uses an endoscopic linear stapler to cut the pancreatic parenchyma, so it is likely to be more convenient than conventional methods and can be used universally.

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**Keywords** Pancreaticoduodenectomy, Stapler method, Postoperative pancreatic fistula, Randomized control trial

## Background

Pancreaticoduodenectomy (PD), which is performed for malignant and borderline-malignant diseases in the pancreatic head and periampullary region, is a highly difficult and invasive surgery [1]. Clinically-relevant postoperative pancreatic fistula (CR-POPF) after PD varies in incidence between 5% and 20% and is associated with a high incidence of life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, or sepsis [2–6]. Several significant randomized controlled trials focused upon operative techniques of pancreatoenteric anastomosis have sought to reduce the incidence of CR-POPF after PD. These include studies comparing invagination vs. duct-to-mucosa anastomosis, pancreatojejunostomy (PJ) vs. pancreaticogastrostomy PG, internal vs. external stent, and also no stent vs. external stent [3, 7–12]. However, the rates of CR-POPF have continued to remain high at 10-20% in most prospective studies [12, 13]. Improving the PJ technique to reduce CR-POPF is therefore an important issue.

PJ has two important aspects: resection and suturing. The resection method for pancreatic parenchyma during PD might affect the incidence of CR-POPF. However, while several randomized controlled trials have focused upon the suturing technique in PJ, no clinical trials have focused on resection of pancreatic parenchyma during PD. Resection of the pancreatic parenchyma during PD has generally been performed with a scalpel or an energy device such as ultrasonic coagulation cutting device. However, the conventional method might cause bleeding from the transverse pancreatic artery running in the pancreatic parenchyma or destruction of pancreatic parenchyma. In particular, suture hemostasis is usually performed for hemorrhage from the cutting surface of pancreatic parenchyma. The pancreatic parenchyma is fragile tissue, so thread tensioning caused by ligation might lead to damage to the pancreatic parenchyma, which can cause CR-POPF. On the contrary, in the pancreatic resection method using surgical stapler, this transverse pancreatic artery is also transected and sutured, so it might help to control arterial bleeding from the stump. Almost no additional suture hemostasis is required, so the pancreatic parenchyma is not damaged in hemostatic manipulation. No prospective studies examining pancreatic parenchymal transection during PD have compared conventional methods vs. surgical stapler with the aim of reducing CR-POPF after PD. In this randomized clinical study, we aim to evaluate the safety and efficacy of using a surgical stapler in comparison with the conventional method during PD, with a specific interest in the rates of CR-POPF.

## Methods/design

### Design

STRAP-PD is a single center, randomized, controlled trial aiming is to demonstrate the superiority of surgical stapler for transection of the pancreatic parenchyma during PD compared with conventional methods using a scalpel, ultrasonic coagulation cutting device or vessel sealing system. Patients with soft pancreatic parenchyma are randomized into control arm A (conventional method) or study treatment arm B (surgical stapler method) depending on what is used for transection of the pancreatic parenchyma during PD. We seek to demonstrate the superiority of the surgical stapler method by comparing the rates of grade B/C postoperative pancreatic fistula (POPF).

The STRAP-PD trial is being conducted at Wakayama Medical University, which has been board-certified as a training institution by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. To ensure the high quality of the study, all operations are performed by instructors and expert surgeons certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

### Randomization

A flow diagram of the STRAP-PD trial is shown in Fig. 1. Randomization will be performed using the randomization schedule retained in the enrollment office and will be completed by the start of surgery. After confirmation of eligibility, including written informed consent, patients will be randomized in a 1:1 allocation ratio to either arm A (conventional method) or arm B (surgical stapler) with a random block size. Random allocation is performed using an allocation table stored by the enrollment office, and assignments are made randomly before the start of the surgery. The allocation table is generated using a permutation block method with a block size of 6, based on the following allocation adjustment factors. The enrollment office securely stores the allocation table in a lockable cabinet to prevent external leakage. The allocation adjustment factors are surgical approach (open surgery/minimally-invasive surgery) and preoperative

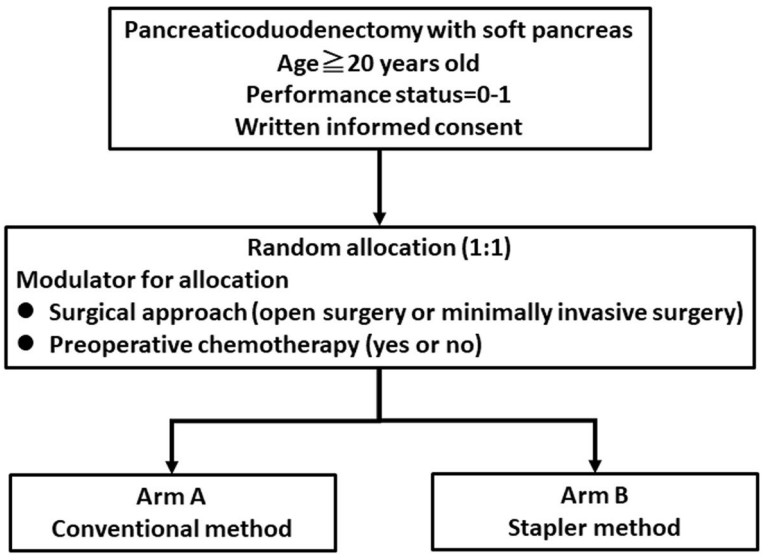


**Fig. 1** Flow diagram of the STRAP-PD (Stapler method for transection of the pancreatic parenchyma during pancreatoduodenectomy) trial

chemotherapy (yes/no). All patients are blinded to the surgical method they will receive, and they are required to sign an informed consent form before enrollment in the study. Blinding of the surgeons is not possible because of the different method used during the operation. Assessment of the result will be made by an independent researcher who will be blinded to the surgical method.

## Interventions

### *Study treatment arm (surgical stapler method)*

Surgical stapler (Endo GIA™ Ultra Universal Staplers or Signia™ Stapling System, Medtronic, Minneapolis, MN) is used for transection of the pancreatic parenchyma during PD. The surgeon should select the optimal cartridge for the automatic suture. The stapler is not released immediately after firing; the jaws of the stapler are held shut for 1 min [14].

After the main pancreatic duct is identified by intraoperative echo, the staples at the main pancreatic duct are manually removed on that site alone and a 5 Fr pancreatic duct tube is placed to secure the main pancreatic duct. The main pancreatic duct should be visually confirmed before pancreatojejunostomy. In order to ensure a landing area for the suture when performing duct -to-mucosa in pancreatojejunostomy, we first confirm the position of the main pancreatic duct using intraoperative ultrasound, and then remove the staples according to the size of the main pancreatic duct.

When severe bleeding from the end of the remnant pancreas is observed, additional hemostasis is performed with a surgical clip, or suture hemostasis using a 5-0 PROLENE™ sutures which are non-absorbable threads composed of polypropylene (a synthetic linear polyolefin; Johnson and Johnson Co., Tokyo, Japan). As additional hemostasis for bleeding at the pancreatic transection margin might affect the incidence of pancreatic fistula, the data for hemostatic suturing will be recorded for statistical analysis of this study. When the parenchyma is crushed or lacerated during the stapling procedure, and then, the surgeon judge that additional sutures to repair the parenchyma or additional resection by stapler closure would be required, these treatments will be acceptable, not a protocol violation. However, the data regarding these treatments will be documented for comprehensive reporting and clarity in study design and statistical analysis, as serious crush or laceration of the remnant pancreas clearly affects the postoperative course.

Repeat transection by evaluation of intraoperative frozen section might affect the incidence of pancreatic fistula, especially in surgical stapler method group. If additional resection is required because of positive margin as assessed by intraoperative frozen section, additional resection of the remnant pancreas would be permitted in the stapler group. However, if additional stapler method is not possible, the case is considered ineligible. Therefore, the data for repeat transection as assessed by intraoperative frozen section will be also recorded for statistical analysis of this study.

In this study, protocol treatment by stapler closure technique is completed, when the pancreatic parenchyma can be tightly clamped with a stapler during pancreaticoduodenectomy, and the pancreatic parenchyma can be resected. Cases in which the pancreatic parenchyma was

too hard or thick to be stapled at the time of pancreatic resection were defined as a deviation. The thickness of the pancreatic parenchyma will be measured at the time of pancreatic resection and the data will be recorded. These data will be analyzed to evaluate the risk of pancreatic fistula and the safety of the stapler method.

#### *Control arm (conventional transecting method)*

In conventional transecting methods, the pancreatic parenchyma is transected using a scalpel, ultrasonic coagulation cutting device or vessel sealing system. In this procedure, a surgical loop is used to gently tie on the remnant pancreas side to prevent bleeding from the remnant pancreatic stump. For arterial bleeding from the remnant pancreatic stump, a 5-0 proline thread is used for suture hemostasis. The main pancreatic duct is visually confirmed and secured by placement of a 5 Fr pancreatic duct tube.

#### *Study endpoints*

The primary endpoint is the incidence of grade B/C POPF within 90 days from the date of surgery. POPF is defined according to the 2017 International Study Group of Pancreatic Surgery (ISGPS) criteria [15]. Secondary endpoints are the incidence of other postoperative complications, which are graded by Clavien-Dindo classification within 90 days from the date of surgery [16]. Furthermore, we evaluate the frequency of residual pancreatitis, pancreatic endocrine function, and pancreatic exocrine function.

### Statistical analysis

#### *Sample size*

In our previous study, the rate of grade B/C POPF rates after PD was 20% for patients with soft pancreas [3]. The rate of grade B/C POPF in arm A using a scalpel, ultrasonic coagulation cutting device or vessel sealing system was therefore estimated to be 20% ($P_A = 0.20$). The rate of grade B/C POPF using surgical stapler in the study treatment (arm B) group was estimated to be 5% ($P_B$=0.05) because it occurred in one of the 20 patients treated in a pilot study by the surgical stapler at our institution [17]. The difference in rates of grade B/C POPF is therefore calculated as $P_A$- $P_B$=0.15. When assessing the unilateral alternative hypothesis $H_1$ "the rates of grade B/C POPF in the arm A and arm B differs" against the null hypothesis $H_0$ "the rates of grade B/C POPF in the arm A and arm B is the same" using the test of population proportion at the $\alpha$=0.05 level of significance, the minimum sample size required for the power 100 (1-$\beta$) of more than 80% is a total sample size of 146 cases (with 73 cases in each group) in two groups. Furthermore, approximately 10% of the patients are expected to be ineligible for surgery, so the cumulative target sample size is set at 160 cases, with 80 cases in each group. These parameters will be documented for comprehensive reporting and clarity in study design and statistical analysis.

#### *Statistical analysis plan*

The primary objective of this study is to evaluate whether the use of surgical stapler to resect pancreatic parenchyma reduces grade B/C POPF compared with the conventional method. In the assessment of the primary endpoint, if the *p*-value falls below the significance level of 0.05, and the occurrence frequency of POPF in the experimental treatment group is lower than that in the conventional method group, it will be a demonstration of the superiority of the stapler method in resection of pancreatic parenchyma. In such a case, we could conclude that pancreatic transection with the surgical stapler is a more beneficial method. If no statistically significant difference is observed between the two groups, the conventional procedure would continue to be considered the standard method for pancreatic transection. The primary analysis will employ the Mantel-Haenszel test, with adjustment factors being allocation adjustment and treatment as a covariate, using the full analysis set. Construction of 95% confidence intervals for the incidence rates of POPF in each group will utilize the Clopper & Pearson exact method. These details will be documented to ensure a comprehensive presentation of the study design, statistical analysis, and interpretation of results.

#### *Study population*

Eligible patients are those scheduled for PD in our department without a dilated main pancreatic duct (MPD) (<5mm), parenchymal atrophy or pancreatitis according to the preoperative enhanced computed tomography. Pancreatic texture is assessed as soft pancreas or hard pancreas using preoperative enhanced CT imaging by radiologists. We will verify whether preoperative assessment of pancreatic texture using CT is consistent with the intraoperative judgment regarding pancreatic texture. The patients with dilated pancreatic duct due to obstruction by tumor or pancreatic atrophy, which might reflect hard pancreas, are not eligible. In addition, if the surgeons determine during operation that the pancreas parenchyma is hard and that a staple is not applied to resect pancreatic parenchyma, the case will be considered ineligible as discontinuation of protocol treatment. Both open surgery and minimally invasive procedures (including robot-assisted approaches) are acceptable.

#### *Inclusion criteria*

1) Patients judged to have soft pancreas among those scheduled for pancreaticoduodenectomy.
2) The thickness of the pancreatic parenchyma can be cut with surgical stapler.
3) ECOG Performance Status (PS) is 0-1.
4) Age 20 years or older.
5) The functions of major organs (bone marrow, heart, liver, kidneys, lungs, etc.) are maintained.
6) Sufficient judgment to understand the content of the research and providing written informed consent.

#### *Exclusion criteria*

1) Serious ischemic heart disease.
2) Complication of liver cirrhosis or active hepatitis.
3) Dyspnea requiring oxygen administration due to interstitial pneumonia or pulmonary fibrosis.
4) Undergoing dialysis for chronic renal failure.
5) Requiring combined resection of surrounding organs.
6) Considered to require arterial reconstruction of the superior mesenteric artery, common hepatic artery, celiac artery, etc.
7) Active double cancers that may affect adverse events or overall survival.
8) Long-term oral steroid use that may cause adverse events.
9) Psychosis or psychiatric symptoms judged to potentially cause difficulty in participation in the study.
10) History of abdominal operation including gastrectomy, colectomy, rectal resection, hepatectomy, but excluding cholecystectomy.
11) Inability to use both iodine-based drugs and gadolinium-based drugs due to serious drug allergies.

### Common to both groups (allowable procedures)

#### *Operative procedure*

In our standard procedure, the stomach is divided just proximal to the pylorus, preserving over 95% of the stomach. If the patient has a malignant disease, lymph nodes are dissected from the hepatoduodenal ligament, around the common hepatic artery, the superior mesenteric artery, and the pancreatic head. Reconstruction is Billroth II reconstruction. The retained jejunum is passed through the transverse mesocolon, and an end-to-side pancreatojejunostomy is performed, followed by an end-to-side hepaticojejunostomy, and finally an antecolic end-to-side gastrojejunostomy [3, 18].

#### *Pancreatojejunostomy procedure*

Anastomosis is performed in a duct-to-mucosa fashion using a single layer of interrupted 5–0 PDS-II® (double-armed, polydioxanone suture; Johnson and Johnson Co., Tokyo, Japan) with eight or more sutures. A 5-Fr polyethylene pancreatic stent tube (Akita Sumitomo Bake, Akita, Japan) is trimmed to a length of 5 cm and positioned at the pancreaticojejunal anastomotic site as an internal stent. If the main pancreatic duct is too large or too small for a 5-Fr stent tube, no stent is placed [3].

Suture of pancreatic parenchyma and jejunal seromuscular layer is performed by modified Blumgart mattress method.

#### *Postoperative management*

This study does not plan to provide medical procedures beyond the routine practice. All patients receive treatment based on the standardized postoperative management protocol for PD [5, 19]. The management of the drain and measurement of amylase levels in the drainage fluid are as follows: 1 BLAKE Silicone Drain 10 mm Flat type® (Ethicon, Inc., Somerville, NJ) is placed near the pancreatic anastomosis. The drain is removed on postoperative day 4 if the drainage fluid is clear, and if pancreatic fistula and bacterial contamination are absent. Amylase level in the serum and the drainage fluid will be routinely measured on postoperative days 1, 3, and 4 [5]. Combination therapies and supportive care including antibiotics and proton-pump inhibitors products that may be used in intraoperative and postoperative management are not specified. Octreotide prophylaxis should not be given.

#### *Standardization and validation of interventions*

In this trial, to guarantee the quality of operative procedure, an advanced skill specialist certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery will perform operation as the surgeon or teaching assistant. Intraoperatively, remnant pancreatic stump after pancreatic transection will be photographed with a digital camera immediately in both groups. Central judgment will be conducted for all of the registered patients by two members. If the procedure of pancreatic transection is not appropriate according to the protocol treatment, the case will be excluded as the one that deviates from the protocol.

### Recruitment

This clinical study will be conducted between September 2023 and December 2027 at a single institute: Wakayama Medical University Hospital. Prior to the start of the study, the treating physician shall provide patients with an easy-to-understand explanation and give them time to contemplate, and request the patients to participate in

| | STUDY PERIOD | | | | |
|---|---|---|---|---|---|
| | Enrollment | Allocation | Post allocation | | Close-out |
| **TIME POINT** | -28days | 0 | Surgery | 90 days | |
| **ENROLLMENT:** | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| Allocation | | X | | | |
| **INTERVENTIONS:** | | | | | |
| Conventional method | | | X | | |
| Stapler method | | | X | | |
| **ASSESSMENTS:** | | | | | |
| Postoperative pancreatic fistula | | | ← | → | |
| Postoperative residual pancreatitis | | | ← | → | |
| Adherence of the residual pancreas and reconstructed intestinal tract assessed by CT | | | | X | |
| Pancreatic endocrine and exocrine function | | | | X | |
| Mortality associated with surgery | | | ← | → | |
| Pathological findings | | | | X | |
| Postoperative hospital stay duration | | | ← | → | |
| Overall postoperative complications | | | ← | → | |

**Fig. 2** Study calendar

the study based on a thorough understanding of the content of the study. The informed consent form shall include the name of the physician who provides the explanation, the name of the patient who provides informed consent, and the date of obtaining informed consent, and it will be signed by both the physician and the patient. Then, one copy is generated to be handed over to the patient and the original copy of the informed consent form is stored in the specified storage site.

### Criteria for discontinuation/completion of protocol treatment

The protocol treatment will be completed with the anastomosis of the pancreas and gastrointestinal tract (pancreaticojejunostomy) following PD. Follow-up will be performed up to 90 days after surgery.

If the protocol treatment cannot be continued for the following reasons, it should be discontinued for the following listed reasons:

1) The patient requests withdrawal from the study.
2) Peritoneal or liver metastasis is found after laparotomy and PD is not performed.
3) Changes in surgical technique during surgery, such as combined resection of other organs, bypass surgery, and exploratory laparotomy.
4) Forced closure without completing the protocol treatment due to an emergency that prevents continuation of the operative procedures (e.g., myocardial infarction, major bleeding, or cardiac arrest due to neural reflex).
5) The surgeon judges the use of medical staplers to be difficult during surgery (e.g., due to thick pancreatic parenchyma).

### Follow-up after completion of treatment (postoperative day 90)

The schedule of this trial is shown in Fig. 2. The day of surgery is set as Day 0, and testing may be performed between two weeks before and after postoperative day 90. The following items are examined, observed, and investigated 90 days after surgery:

1) Postoperative complications: presence or absence and grades of pancreatic fistula, delayed gastric emp-

tying, and intraabdominal bleeding (assessed according to the ISGPS criteria), and presence or absence and severity of all postoperative complications (assessed according to the Clavien-Dindo classification)
2) Rate of postoperative remnant pancreatitis (post-pancreatectomy acute pancreatitis classification by ISGPS [20].
3) Adherence between the remnant pancreas and the reconstructed intestine as well as the extent of pancreatic duct dilatation on CT.
4) Endocrine and exocrine pancreatic function.
5) Operative mortality up to 30 days and 90 days after surgery.
6) Degree of residual tumor (R0/R1).
7) T, N, M stages according to the eighth edition of the UICC-TNM classification.
8) Postoperative hospital stay (time from the day of surgery to the day of discharge when the day of surgery is indicated as Day 0).

### Data and safety monitoring

During the study, monitoring for the safety of the trial subjects regarding inclusion/exclusion criteria, qualitative analyses of feasibility, and adverse events will be performed once a year by an independent data monitoring committee. The monitoring committee will also report the serious adverse events to the committee of efficacy and safety assessment. If the occurrence of serious adverse events after the start of the trial indicates a potential health hazard caused by the study treatment, deliberation regarding early termination of the entire study between the committee of efficacy and safety assessment and the principal investigator will be required. When the entire study will be discontinued, the principal investigator must request a review by Wakayama Medical University.

### Ethics review board

All investigators related to this study will conduct this study in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labor and Welfare of Japan. The protocol has been approved by the Wakayama Medical University Hospital Institutional Review Board (approval number 3923). The trial protocol has also been registered in the protocol registration system at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000052089). The registration date was 1st September 2023. Prior to the start of the study, the investigator shall provide the patients with an easy-to-understand explanation using the written informed consent form regarding the content of the study including design and rationale of this study, protocol treatment, expected effect of protocol treatment, expected adverse events, potential benefits and disadvantages of participating in the study, cost burden and compensation, refusal and withdrawal of consent, etc.

### Dissemination policy

Based on dissemination policy, The protocol of the STRAP-PD trial was registered at University Hospital Medical Information Network Clinical Trials Registry to ensure disclosure of clinical trial information, transparency and accountability in this trial. The results of the STRAP-PD trial will be submitted to a peer-reviewed journal regardless of the trial outcomes. Authorship will be defined based on four criteria: substantial contributions, drafting, approval, and accountability in accordance with the STRAP-PD trial publication policy and international guidelines.

## Discussion

This randomized controlled trial will investigate the safety and efficacy of use of surgical stapler for transection of the pancreatic parenchyma during pancreaticoduodenectomy as compared to a conventional method using a scalpel, ultrasonic coagulation cutting device or vessel sealing system. The application of surgical stapler for pancreatic parenchyma during PD remains uncommon, despite becoming nearly universal for stump closure during distal pancreatectomy in real-world practice. Only one report regarding pancreatic parenchymal transection using surgical stapler during PD has been previously published, which demonstrated that the rate of pancreatic fistula Grade B or C was 5.9% (one patient developed Grade B pancreatic fistula in 17 patients treated) [21]. However, in the study, pancreatic parenchymal transection using surgical stapler has been performed in limited number of patients. There are currently no prospective comparative studies of pancreatic parenchymal transection during PD using conventional methods vs. using surgical stapler with attention to the potential reduction of CR-POPF after PD.

There might be two problems in using surgical stapler during PD. When suturing the main pancreatic duct during PJ, it is necessary remove the staple at the site of staple line to find the main pancreatic duct. The other problem is that closure of the main pancreatic duct with the surgical stapler may induce pancreatitis of the remnant pancreas. Postoperative obstructive pancreatitis was reportedly associated with an increased occurrence of CR-POPF [20]. There are no prospective comparative studies that investigate the safety and efficacy of the surgical stapler in resection of the pancreatic parenchyma

during PD. Prior to this randomized controlled trial, to evaluate the safety and efficacy of surgical stapler, we prospectively used the surgical stapler for pancreatic parenchymal transection in 20 consecutive patients with soft pancreas [17]. In the pilot study, only one patient (5%) developed pancreatic fistula of ISGPF Grade B, and the results showed potential benefits of using the surgical stapler for pancreatic parenchymal transection during PD to reduce the occurrence of CR-POPF. Reasons for the lower incidence of clinically relevant POPF by using surgical stapler might include reliable closure of branched pancreatic ducts and reduced parenchymal damage due to suture hemostasis by preventing bleeding from the pancreatic stump or adhesion between staples and the jejunal serosa.

The control arm in this study has variable methods of pancreatic transection. Because, minimally invasive surgery (laparoscopic or robot assisted) is applied in this study. In minimally invasive surgery, resection with a scalpel is often difficult to control bleeding from pancreatic stump. A scalpel, ultrasonic coagulation cutting device or vessel sealing system has been universally used to resect pancreatic parenchyma during pancreaticoduodenectomy all over the world. For these reasons, the methods to resect pancreatic parenchyma in the conventional methods for the control arm were not limited to one method, but some conventional transecting methods were applied for this study. Moreover, assumption of a 20% incidence of POPF in the control arm of this study are based on the incidence of pancreatic fistula by these conventional transecting methods.

The subjects of this study were only patients with soft pancreas, cases with hard pancreas were excluded. We excluded cases with hard pancreas for two reasons in this study. First, the risk of developing a pancreatic fistula is extremely low in cases with hard pancreas. The rate of pancreatic fistula in our department has been very low in patients with the hard pancreas, even when using the conventional method. The rate of CR-POPF 0% in patients with hard pancreas and 15% in patients with soft pancreas in previous clinical studies in our institution [3]. The soft pancreas has been reported to be a risk factor for the development of CR-POPF, and the rate is as high as approximately 20 to 40% [3, 17, 22, 23]. Conversely, the rate in the hard pancreas is reported at approximately 0 to 10% [3, 12, 17, 22]. Second, the use of staples is limited in cases with hard pancreas. Transection by surgical stapler is not recommended in cases with hard pancreas because of the possibility of damage to the pancreatic parenchyma [18]. Therefore, in patients with hard pancreas, transection of hard pancreatic parenchyma by using a staple is not feasible. Moreover, patients with a dilated pancreatic duct were excluded from this study. In this study, a dilated pancreatic duct was defined as a main pancreatic duct measuring ≥5 mm on preoperative imaging. The reason is that a dilated pancreatic duct ≥5 mm reflects a hard pancreas and is associated with a low risk of developing a clinically significant pancreatic fistula [24].

In addition to the pancreatic parenchyma, there are many risk factors for the development of pancreatic fistula. Some studies have reported that pancreatic fistula risk score can predict the development of postoperative pancreatic fistula [25–27]. Therefore, we plan to collect these factors, calculate a pancreatic fistula risk score, and evaluate whether the characteristics of pancreatic fistula between the two groups are similar.

In this study, surgical stapler (Endo GIA™ Ultra Universal Staplers or Signia™ Stapling System, Medtronic, Minneapolis, MN) is used for transection of the pancreatic parenchyma during PD. Although the difference between two types of stapler device is that the former is a manual system and the latter is an electric system, the stapler in both instruments is not released immediately after firing; the jaws of the stapler are held shut for 1 min. Firing performance is completely similar between both instruments. Selection of two types of stapler device depends on surgeon's preference. However, we believe that the difference between the two types of stapler device doesn't affect the occurrence of pancreatic fistula. Moreover, the size of stapler cartridges is intraoperatively decided by surgeons according to the thickness of the pancreatic parenchyma. That is, the optimal staple height might be selected to avoid pancreatic parenchymal crush or lacerations and obtain proper closure [28].

We acknowledge that a single-center study design may limit the generalizability of the results. However, the stapler technique has not yet been widely adopted in many centers, and its effectiveness remains unknown. Although we designed this study as a single-center trial, we understand the value of a larger cohort or multicenter approach. As a next step, if the primary endpoint of this study is achieved, a large multicenter study will be required to confirm the endpoints. Also, this study is not blinded; however, due to the different methods used during surgery, it is not possible to blind the surgical methods. In order to reduce open-blind bias, outcome assessment will be performed by an independent investigator blinded to the surgical method.

The study intervention might reduce the rate of CR-POPF after PD and could contribute to the improvement of postoperative short outcomes and quality of life after PD if the usefulness of surgical stapler can be demonstrated. In case of malignant disease, this may also lead to the early induction of the postoperative adjuvant chemotherapy to improve prognosis. In addition, in recent

years, minimally invasive surgery has been increasingly used in PD. Transection of the pancreas by surgical stapler might be convenient in minimally invasive surgery, but the safety has not been prospectively investigated. The transection methods based on the experience of the surgeon remains to be adopted in each institution. Therefore, this study may also greatly contribute to minimally invasive pancreatic surgery if it can demonstrate the usefulness of the surgical stapler for transection of pancreatic parenchyma during PD.

## Trial status

The STRAP-PD trial was opened in September 2023. At the time of submission of this paper (June 2024), the protocol is version 1.1. The completion date is estimated to be December 2027.

**Abbreviations**

| | |
|---|---|
| ECOG | Eastern Cooperative Oncology Group |
| ISGPS | International Study Group of Pancreatic Surgery |
| PD | Pancreaticoduodenectomy |
| POPF | Postoperative pancreatic fistula |
| UICC | The Union for International Cancer Control |

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**Authors' contributions**

YK and MK drafted the manuscript. MK is the principal investigator for the study. YK and MK are responsible for the concept and design. YK, AS, AT, HM, SH, AM, TY, MS, KM and MK made significant contributions to the protocol validity, design, and drafting and revision of the manuscript. YK developed the statistical considerations for the trial. All authors contributed to the scientific accuracy of the manuscript and read and approved the final manuscript.

**Funding**

The study will be funded by Medtronic. All medical costs related to this study will be covered by the health insurance as the routine practice and patients will pay out-of-pocket costs for observations, tests, radiotherapy, and other drugs used during the clinical study.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Data availability**

The data that support the findings of this study are not openly available due to reasons of sensitivity, but are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**

All investigators involved in this research will conduct this study in accordance with the Declaration of Helsinki and the Ministry of Health, Labour and Welfare of Japan Ethical Guidelines for Clinical Studies. The protocol has been approved by the Wakayama Medical University Hospital Institutional Review Board (approval number 3923) and in the protocol registration system at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000052089). All subjects for this study will be provided with a consent form describing this study and containing sufficient information for them to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the institutional review board for the study.

**Consent for publication**

Not applicable.

**Competing interests**

The study will be funded by Medtronic. All medical costs related to this study will be covered by the health insurance as the routine practice and patients will pay out-of-pocket costs for observations, tests, radiotherapy, and other drugs used during the clinical study.

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