Randomised Controlled Trial

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Laparoscopic versus open pancreatoduodenectomy for periampullary tumors: a randomized clinical trial

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Background: There is a lack of robust evidence on the efficacy of laparoscopic pancreatoduodenectomy compared to open surgery. This study was aimed to compare time to functional recovery (FR) between laparoscopic and open pancreatoduodenectomy.

Materials and methods: This pragmatic, multicenter, randomized controlled phase 3 trial was conducted in seven tertiary centers. Patients with periampullary tumors were randomized using a block design in a 1:1 ratio and stratified by pancreatic fistula risk. Participants were randomized to undergo open or laparoscopic pancreatoduodenectomy by expert pancreatic surgeons. The primary outcome was the time to FR, defined as the number of days until FR was achieved in all five domains. The secondary endpoints included perioperative and short-term oncological outcomes.

Results: Between March 2019 and June 2022, 252 patients were randomly assigned to laparoscopic ($n = 125$) or open groups ($n = 127$). Primary outcomes were reported in 235 patients. The mean time to FR was shorter in laparoscopic group compared to the open group (7.7 vs. 9.0 days, $P = 0.03$). Laparoscopic group exhibited a higher cumulative rate of FR compared to the open group (Hazard ratio,1.34; 95% CI, 1.03–1.74; $P = 0.02$). Severe complications, R0 resection, the number of retrieved lymph nodes and short-term survival rates were comparable between the two groups.

Conclusions: Laparoscopic pancreatoduodenectomy demonstrated modest advantages in FR time over open surgery for selected patients with experienced surgeons.

Keywords: functional recovery, laparoscopy, pancreatoduodenectomy

Introduction

Periampullary tumors are a group of diseases that occur in the head/uncinate process of the pancreas, distal bile duct, ampulla, and duodenum. Pancreatoduodenectomy, a surgical treatment that involves resection of the duodenum, pancreatic head, and bile duct, is the standard approach for these neoplasms. However, pancreatoduodenectomy is a complex procedure with high morbidity and mortality rates. With advancements in laparoscopic surgery to decrease postoperative morbidity, it is now being applied to pancreatoduodenectomy as well[1]. However, the uptake of laparoscopic pancreatoduodenectomy has been slow because the procedure presents considerable technical challenges compared to open surgery[2,3]. In addition to

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the difficult procedure, problems such as implications for selective patients, and high morbidity in early experiences were reported[4]. Recent studies have demonstrated the advantages of laparoscopic pancreatoduodenectomy over open surgery, including a shorter hospital stay and less blood loss without compromising other outcomes[5–12]. However, most of these studies are retrospective, and only five randomized controlled trials have been conducted by experienced laparoscopic surgeons[13–17], and one propensity score-matched analysis was reported[1]. Although some of these trials report a short hospital stay without compromising the main clinical outcome, they are underpowered and they used the hospital stay as the main outcome, which is a surrogate indicator for postoperative discharge readiness and physical recovery, rather than the actual health status of the patients[18,19]. Although one randomized trial used functional recovery focused on patient well-being as the primary outcome, the study was prematurely terminated due to safety concerns[15].

Therefore, we conducted a multicenter, randomized trial to compare functional recovery as the primary end point between laparoscopic and open surgeries, with postoperative and short-term oncological outcomes of malignant periampullary tumors as secondary endpoints.

HIGHLIGHTS

- This is randomized controlled trial on laparoscopic versus open pancreatoduodenectomy that was completed with patient-focused functional recovery as a primary outcome.
- Laparoscopic group demonstrated a shorter time to functional recovery, and a higher cumulative rate of functional recovery compared to that in open surgery group.
- Laparoscopic surgery showed comparable immediate postoperative complications and oncologic outcomes compared to open surgery.

Methods

Trial design

This was a multicenter, randomized controlled trial comparing functional recovery in patients with periampullary tumors who underwent either laparoscopic or open pancreatoduodenectomy. The trial was conducted at seven medical centers. The trial protocols were approved by the institutional review board at each medical center (IRB No. 2018-0687). The trial was conducted in accordance with good clinical practice guidelines and adhered to the principles outlined in the Declaration of Helsinki and CONSORT, Supplemental Digital Content 1, http://links.lww.com/JS9/D343 guidelines[20]. Patients and surgeons were not blinded in accordance with the recommendation of the safety monitoring board for this study. The committee decided against conducting a blinded trial due to concerns that blinding may pose potentially fatal risks to patients. Outcomes were measured by assessors who were not involved in the study to enhance objectivity. Data and safety were independently monitored by the caretakers masked to randomization. Full trial details are available in the study protocol (SDC 1, ClinicalTrials.gov Identifier: NCT03870698, Supplemental Digital Content 2, http://links.lww.com/JS9/D344).

Participants

The trial enrolled patients aged 19–80 years who had periampullary tumors around the pancreas, distal bile duct, ampulla, and duodenum and were eligible for pancreatoduodenectomy, with an Eastern Cooperative Oncology Group score of 0–2[21]. Main exclusion criteria included the involvement of major blood vessels (superior mesenteric vessels, common hepatic artery, celiac axis), distant metastasis, prior chemotherapy, systemic disease that would interfere with this study[22]. Detailed information regarding the inclusion and exclusion criteria is listed in the protocol (SDC 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D344). All participants were provided with written informed consent before enrollment. Eligible patients were initially identified at each center and their eligibility was confirmed by the centralized safety committee.

Randomization

Randomization was performed with a 1:1 ratio using a computerized random number generator with a random block size of six by the independent statistician. The concealed allocation file was provided to independent coordinators at each hospital, who verified assignments as new participants were enrolled. Patients were stratified based on preoperatively estimated risk of postoperative pancreatic fistula. A high risk of postoperative pancreatic fistula was defined when the BMI was more than 25 kg/m^2 or pancreatic duct size was 3 mm or less based on the preoperative predictive score of pancreatic fistulas developed by Robert and colleagues and previous trials[15,18].

Surgical interventions

The techniques for laparoscopic and open procedures were previously described in other sources[9,23,24]. Laparoscopic-assisted or robot-assisted pancreatoduodenectomy was excluded to eliminate potential bias. Resection and anastomosis followed the same operative principles, and the detailed procedures depended on the manner of each center. Pancreatic reconstruction was done using a two-layer duct-to-mucosa pancreatojejunostomy. Conversion to open surgery was defined as any skin incision required for reasons other than trocar placement or specimen removal. Pain was managed using intravenous patient-controlled analgesia, which was usually discontinued on the fourth day after surgery; thereafter, oral, or patch-type analgesics were administered as needed. Intravenous or intramuscular analgesics were administered when pain, as assessed by a numeric rating scale, exceeded 4 points. Patients were advised to visit the outpatient clinic two weeks after discharge and every three months for tumor markers and radiologic examinations to check for any signs of recurrence. The participating surgeons included surgeons with experience in performing more than 500 open pancreatoduodenectomies and 150 laparoscopic pancreatoduodenectomies, and surgeons with experience in performing more than 100 open procedures and between 20 and 100 laparoscopic pancreatoduodenectomies. Unedited and edited operation videos were periodically reviewed during regular meetings at each participating center. Experiences with laparoscopic procedures were also shared by the Korean Study Group of Minimally Invasive Pancreatic Surgery, which is a local chapter of the International Minimally Invasive Pancreatic Surgery Society.

Outcomes

The primary outcome was time to functional recovery defined as the number of days from the completion of surgery until functional recovery was achieved in five domains over three consecutive days. Unlike other previous studies[15,25], this study defined functional recovery if the initial functional recovery lasted for three days. This definition was selected because our preliminary experiment documented numerous cases of functional recovery that were not sustained. Data collection and outcome assess were performed by nurses and physicians who were not involved in this study, and assignment information was not provided to data collectors and outcome assessors. Initial functional recovery was defined as meeting all five criteria for restored mobility, adequate pain control, dietary intake, no need for fluid administration, and absence of infection signs. Pain was assessed using a numeric rating scale. Fluid and food intake were monitored, and normal tolerance was defined as the resumption of oral intake of solid food for at least twenty-four hours. Secondary endpoints included perioperative outcomes (operative time, blood loss, transfusion, conversion to open surgery, length of hospital stay, complications, mortality within ninety days of surgery, readmission within two months), oncologic outcomes (R0 resection, number of retrieved lymph nodes, short-term recurrence-free survival, and overall survival rate), and serum cytokine levels. Short- and long-term complications were defined according to established criteria by the Clavien–Dindo classification[26] and the pathological report was documented according to the standards set by the College of American Pathologists. These data were monitored and evaluated by a data and safety monitoring board[27–29]. Oncologic follow-up included imaging and laboratory tests. Continuous measurement of cytokines was based on previous studies, and we investigated whether there was a difference in the extent of cytokine elevation, indicative of the inflammatory response, between the two groups[30,31]. Serum levels of cytokine including interleukin-1β, interleukin-6, and tumor necrosis factor-α were measured on postoperative days one, three, and seven at a single institution using the enzyme-linked immunosorbent assay method following the manufacturer's instructions. Exploratory endpoints included functional recovery for elderly patients more than 65-years-old, surgical indications, presence of postoperative complications.

Statistical analysis

To address potential bias in data analysis, participating faculty only accessed the data after it was finalized, and the database was locked (data closing). This ensured they were analyzing secured data, effectively maintaining blinding for the analysis stage. Full details of the sample size calculations are available in the protocol (SDC 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D344). The sample size was calculated based on the length of hospital stay because there was no prior research on the duration of functional recovery after pancreatoduodenectomy at the time of study design. Based on a systematic review[10], we hypothesized that hospital stay would be related to functional recovery and that functional recovery of the laparoscopic group would be 20% faster than the open group. The two-sided significance level (α) was set at 5%, and the statistical power (1-β) was set at 80%. The final number of subjects required for this study was 126 in each group, and a total of 252 patients were required to confirm a significant difference between the two groups, accounting for a 10% dropout rate. Primary and secondary outcomes were evaluated using a modified intention-to-treat principle and a per-protocol analysis. As there was no adjustment made for multiplicity in the analysis of secondary endpoints, the results of these analyses should be considered exploratory. Safety analysis was performed on all patients who were randomized and underwent surgery. Data are presented as mean with standard deviation for continuous variables and as percentages for categorical variables. The χ^2 test and Student's t-test were used for between-group comparisons. The short-term overall and recurrence-free survival rates were estimated using the log-rank test. The achievement of five domains of functional recovery was presented using a forest plot. Time to functional recovery was estimated and compared using restricted mean survival time based on a previous study[32], and the cumulative incidence rate of functional recovery was determined using the Fine-Gray model with hazard ratio and 95% CI. Sensitivity analysis was performed using an alternative definition, with the first day when all domains were achieved (SDC 2, statistical analysis plan, Supplemental Digital Content 3, http://links.lww.com/JS9/D345) as the primary outcome to assess the robustness of a statistical conclusion. SAS version 9.4 (SAS Institute) and R 4.2.0 (R Foundation for Statistical Computing) were used for analyses.

Results

Participants

Out of 839 patients initially assessed for eligibility between 8 March 2019, and 10 June 2022, 252 patients were randomly assigned to either the laparoscopy group ($n=125$) or the open surgery group ($n=127$). Of these, seven patients did not receive the allocated surgical intervention due to patient withdrawal ($n=4$) or unexpected metastasis before surgery ($n=3$). Ten patients withdrew their consent for the study after the surgery. Therefore, a total of 235 patients who underwent the allocated surgical procedures and reported the primary outcomes were included in the analysis, exceeding the required number of 226 participants. There were 119 patients in the open surgery group and 116 in the laparoscopy group (Fig. 1). Five laparoscopic surgery cases that were converted to open surgery were analyzed in the laparoscopic group. The baseline characteristics of the randomized patients, including age, sex, body mass index, high risk of postoperative pancreatic fistula, and malignant diseases, were similar between the open and laparoscopic groups (Table 1, SDC 3, Supplemental Digital Content 4, http://links.lww.com/JS9/D346, Tables S1–2, Supplemental Digital Content 4, http://links.lww.com/JS9/D346).

Primary outcome

The mean time to functional recovery was 7.7 ± 0.5 days in the laparoscopy group versus 9.0 ± 0.5 days in the open surgery group (mean difference, −1.30; 95% CI −3.07 to −0.08; $P=0.03$). The rate of function recovery at 30 days after surgery was higher in the laparoscopy (100%) group compared to the open (93.3%) surgery group (mean difference, 6.72; 95% CI 2.22–11.22; $P=0.007$, Table 2). Additionally, the cumulative achievement of functional recovery within 30 days was faster in the laparoscopy group compared to the open surgery group (ratio

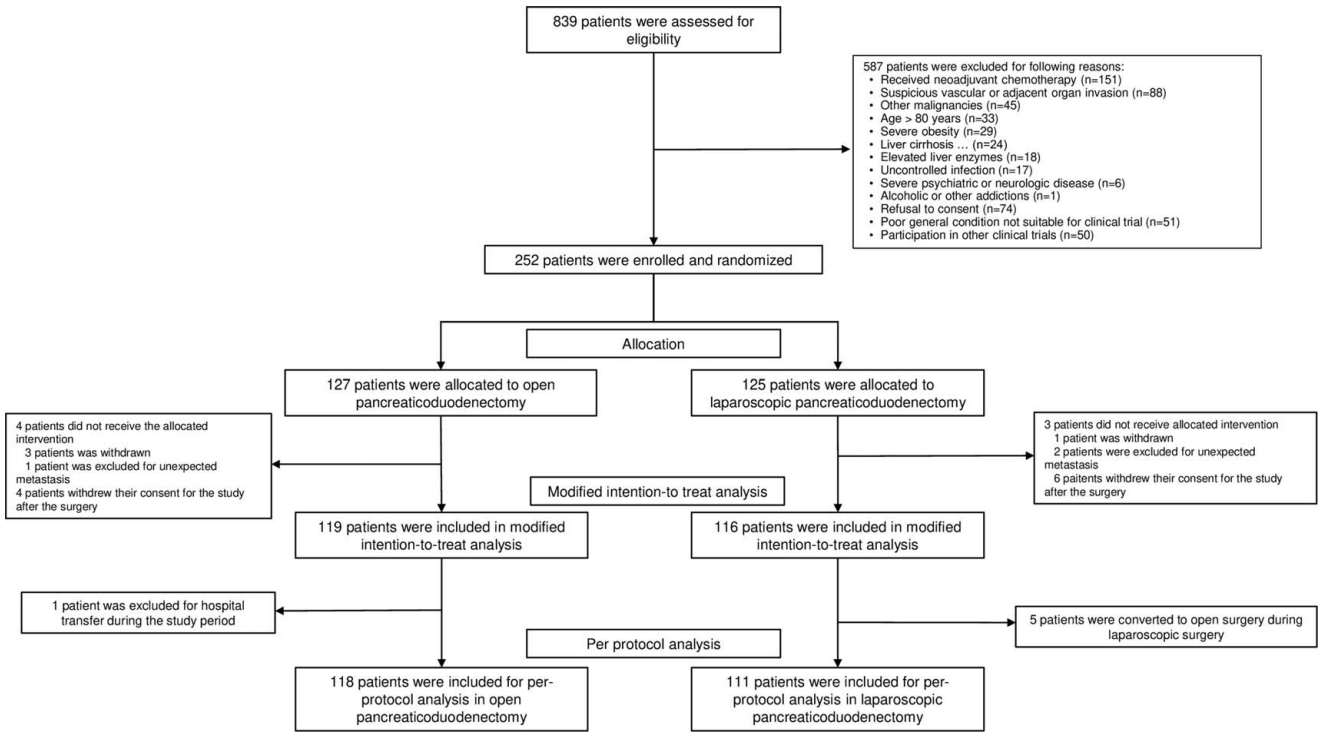

Figure 1. Screening, enrollment, randomization, and follow-up. The primary outcome was analyzed in 235 patients underwent either laparoscopic or open pancreatoduodenectomy in the modified intention-to-treat analysis, which included all patients who underwent randomization and assigned treatment. Per-protocol analysis was performed in 229 patients who completed the study without deviation of randomization treatment.

of instantaneous event rate), 1.34; 95% CI, 1.03–1.74; $P = 0.02$, Figure 2).

Among the five specific domains of functional recovery achieved in laparoscopy and open groups, the laparoscopic group showed better restoration of mobility, caloric intake, and fluid administration compared with the open surgery group. Restored mobility was significantly higher in the laparoscopy group as well (ratio of instantaneous event rate, 1.32; 95% CI, 1.02–1.71; Fig. 3, SDC 3, Table S3, Supplemental Digital Content 4, http://links.lww.com/JS9/D346).

A sensitivity analysis was performed using an alternative definition, where the achievement of functional recovery was defined as the first day of achieving all domains. Here, the laparoscopy group showed a faster time to functional recovery (ratio of instantaneous event rate, 1.35; 95% CI, 1.04–1.75; $P = 0.02$; SDC 3, Figure S1, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). Similar results were shown in per-protocol analysis (SDC 3, Figure S2, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). Exploratory analysis on functional recovery is shown in Supplemental Digital Content 3, Supplemental Digital Content 4, (SDC 3, Figure S3-5, Supplemental Digital Content 4, http://links.lww.com/JS9/D346).

Secondary outcomes

No deaths within 90 days of surgery occurred in either group. Adverse events in the safety analysis are shown in Supplemental Digital Content 3 (SDC 3, Table S4, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). The mean operation time was longer in the laparoscopy group (366 min vs. 298 min), while the two groups showed comparable results in terms of the estimated blood loss (239.0 ml vs. 234.3 ml), length of hospital stay (10.7 days vs. 11.2 days), clinically relevant postoperative pancreatic fistula (11.2% vs. 11.8%), delayed gastric emptying (3.4% vs. 6.7%), postoperative complications greater than grade IIIa (15.5% vs. 15.1%), and 60-day readmission rate (12.9% vs. 13.4%). The R0 resection rate (86.2% vs. 90.2%), and number of retrieved lymph nodes (19.6 vs. 18.3) were similar between the two groups as well (Table 2, SDC 3, Table S6, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). Among 127 patients with periampullary cancers, the short-term overall survival (71% vs. 77.7%) and recurrence-free survival (58.9% vs. 67.2%) were comparable between the two groups during a median follow-up duration of 24.6 months (SDC 3, Figure S6-7, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). There were no significant differences in the levels of interleukin-1β, interleukin-6, and tumor necrosis factor-α on postoperative days 1, 3, and 7 between the laparoscopy and open surgery groups (SDC 3, Table S5, Supplemental Digital Content 4, http://links.lww.com/JS9/D346). We assessed quality of life (QoL) using the EORTC QLQ-C30 instrument in both the preoperative and immediate postoperative states. However, we did not observe any statistically significant changes in QoL component between the two groups.

Discussion

In this multicenter, randomized controlled trial in patients with periampullary tumors, laparoscopic pancreatoduodenectomy had a shorter time (1.3 days) to functional recovery compared to open pancreatoduodenectomy. Sensitivity analysis also

Table 1

Baseline characteristics of all participants who underwent randomization.[a]

	Laparoscopy ($n=125$)	Open ($n=127$)	P
Age, mean (SD), year	62.5 (8.9)	63.2 (10.6)	0.44
Sex, *N* (%)			0.91
Male	71 (56.8)	73 (57.4)	
Female	54 (43.2)	54 (42.5)	
ECOG performance status score, *N* (%)[b]			0.43
0	118 (94.4)	123 (96.8)	
1	6 (4.8)	4 (3.1)	
2	1 (0.8)	0 (0.0)	
BMI, mean (SD)[c]	23.9 (2.7)	23.6 (2.8)	0.49
Comorbidities, *N* (%)	89 (71.2)	101 (79.5)	0.12
Hypertension	46 (36.8)	53 (41.7)	
Diabetes mellitus	37 (29.6)	38 (29.9)	
Etc.	65 (52.0)	69 (54.3)	
ASA risk score, *N* (%)[d]			0.66
1	8 (6.4)	6 (4)	
2	102 (81.6)	104 (82.4)	
3	15 (12.0)	17 (13.6)	
Pancreatic duct size, mean (SD), mm[e]	3.4 ± 2.3	3.6 ± 2.9	0.49
Risk of postoperative pancreatic fistula, *N* (%)[f]			0.73
High	91 (72.8)	90 (70.8)	
Low	34 (27.2)	37 (29.1)	
Indications for surgery, *N* (%)			
Malignant disease	75 (60.0)	65 (51.1)	0.28
Pancreatic cancer	34 (27.2)	24 (18.8)	
Distal bile duct cancer	26 (19.2)	22 (17.3)	
Ampullary cancer	12 (9.6)	18 (14.1)	
Duodenal cancer	3 (2.4)	1 (0.7)	
Benign or borderline malignancy	50 (40.0)	62 (48.8)	0.51
Intraductal papillary mucinous neoplasm	29 (22.4)	40 (31.4)	
Neuroendocrine tumor	10 (8)	11 (8.6)	
Solid pseudopapillary neoplasm	2 (1.6)	3 (2.3)	
Etc.[g]	9 (7.2)	8 (1.2)	
Preoperative quality of life score, mean (SD)[h]	64.2 (23.2)	62.8 (24.9)	0.66
Preoperative biliary drainage, *N* (%)	55 (44.0)	45 (35.4)	0.16
Total bilirubin, mean (SD), mg/dl	1.0 (1.2)	0.9 (1.5)	0.62
Hemoglobin, mean (SD), g/dl	12.8 (1.5)	13.0 (2.5)	0.59
Albumin, mean (SD), g/dl	4.1 (3.5)	3.7 (0.4)	0.08
Carbohydrate antigen 19-9, mean (SD), U/ml	110.3 (303.4)	263.4 (1853.6)	0.35

ASA, American Association of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group.

[a]Plus–minus values are means ± standard deviation. Data are shown dataset, which included participants who underwent open and laparoscopic surgery after randomization. Percentages may not total 100 because of rounding.

[b]Eastern Cooperative Oncology Group performance status score are assessed on a scale of 0 to 5, with higher scores indicating greater disability.

[c]The BMI is the weight in kilograms divided by the square of the height in meters.

[d]The American Association of Anesthesiologists scoring system is used to assess the physical status of patients before surgery; scores range from 1 to 5, with higher numbers indicating a lower likelihood of survival.

[e]Pancreatic duct size was measured using preoperative computed tomography.

[f]Preoperative risk for postoperative pancreatic fistula was evaluated using Roberts model[14] based on body mass index and measured pancreatic duct size on preoperative computed tomography.

[g]Nine patients in laparoscopic group underwent surgery for serous cystic neoplasm ($N=5$), and so on ($N=4$). Eight patients in open group underwent surgery for gastrointestinal stromal tumor ($N=1$), mucinous cystic neoplasm, ($N=2$), serious cystic neoplasm ($N=2$) and so on ($N=3$).

[h]Evaluation of preoperative Quality of life was based on European Organization for Research and Treatment of Cancer- questionnaire 30, which includes five function scales, nine symptoms' scales and a global health status and quality of life scale; results for the global health status and quality-of-life scale and selected function scales are included in this report. Scores on these scales range from 0 to 100 after linear transformation of the raw scores, with higher scores representing better global health status and quality of life.

confirmed this finding. Postoperative and short-term oncologic outcomes were similar between the two groups.

With the advancement of laparoscopic techniques, laparoscopic pancreatoduodenectomies are becoming more common in clinical settings. However, there is still a lack of evidence regarding their safety and effectiveness. Previous randomized trials comparing short-term outcomes have reported mixed results, and most studies have used hospital stay as the primary end point[13–16]. Traditional clinical performance indicators such as length of hospital stay primarily reflect resource and reimbursement-related healthcare standards and are limited in reflecting the actual functional recovery of patients. Patient functional recovery outcomes provide a more comprehensive evaluation of patient care. Our trial shows that laparoscopic pancreatoduodenectomy has a significantly faster time to functional recovery compared to open pancreatoduodenectomy, as measured by multi-modal criteria. Among the five domains of functional recovery, restored mobility was found to be the most significant for laparoscopic pancreatoduodenectomy compared to the other domains. However, the actual reduction in functional recovery time was lower than the anticipated 20% reduction that was used in the sample size calculation. This was partly due to the limited availability of data on functional recovery during the trial design, which resulted in the utilization of hospital stay duration from a previous meta-analysis for determining the sample size. Other randomized studies have reported a median difference of 1 day in hospital stay between laparoscopic and open surgery[16,33–35]. Despite the significant reduction in functional recovery time observed in laparoscopic pancreatoduodenectomy, the smaller-than-expected decrease raises uncertainty regarding its clinical significance.

Debate continues regarding the experience of surgeons in clinical trials and the safe dissemination of laparoscopic pancreatoduodenectomy, which is hindered by steep learning curves and unfavorable early outcomes. Previous studies have shown that 38–60 cases are needed to overcome the learning curve[3,23,24,36,37]. Prior trial (ClinicalTrials.gov number, NTR5689) used 20 cases as entry cut-off and reported higher mortality and open conversion rate[15]. In contrast, another trial with greater than 100 laparoscopic pancreatoduodenectomy experience showed similar morbidity/mortality rates and low open conversion rates[16]. Our trials involved both surgeons with more than 150 cases of laparoscopic pancreatoduodenectomy experience and surgeons who had performed at least 20 laparoscopic pancreatoduodenectomy and had received ongoing education. While utilizing highly experienced surgeons minimizes variations due to a learning curve, it can be challenging to achieve in practice. Therefore, we investigated the potential of surgeons with intermediate experience who benefit from continuous education and mentorship from highly experienced surgeons. Our study involved experienced surgeons from high-volume centers specializing in both open and laparoscopic surgery. No surgeons fell within the specific range of 100–150 laparoscopic pancreatoduodenectomy, although some surgeons surpassed 150 procedures. Accumulating more than 100 cases of laparoscopic pancreatoduodenectomy can be very challenging in actual clinical practice. However, obtaining satisfactory results may be possible with sufficient clinical experience under the guidance of experts at a large medical center with continuous educational programs before reaching that threshold.

The main concerns of laparoscopic pancreatoduodenectomy are the risk of pancreatic fistula and related complications. This trial found similar perioperative outcomes between the two groups when stratified by pancreatic fistula risk. Length of stay was not significantly different between the two groups. Wang *et al.*[16] conducted a randomized trial including a larger number of patients than that included in the present study and reported that the length of stay was significantly shorter in the laparoscopic group by one day. The oncological safety of laparoscopic

Table 2

Primary and secondary outcomes between open and laparoscopic pancreatoduodenectomy groups in modified intention-to-treat analysis.[a]

	Laparoscopy ($n=116$)	Open ($n=119$)	Treatment effect[b] (effect size)	P
Primary outcome				
Functional recovery, mean (SD), days[c]	7.7 (0.5)	9.0 (0.5)	–1.30 (–3.07 to –0.08)	0.03
Achievement of functional recovery in 30 days, *N* (%)	116 (100)	111 (93.3)	6.72 (2.22–11.22)	0.007
Secondary outcomes				
Operation Time, mean (SD), min	366.1 (61.2)	298.2 (55.9)	67.87 (52.78–82.96)	0.001
Blood loss, mean (SD), ml	239.0 (204.9)	234.3 (200.4)	4.68 (–47.42 to 56.79)	0.85
Intraoperative transfusion, *N* (%)	8 (6.9)	7 (5.8)	1.01 (–0.72 to 5.24)	0.75
Hospital stays, mean (SD), day	10.7 (6.4)	11.2 (5.2)	–0.61 (–1.04 to 1.97)	0.54
Extent of resection in malignancies, *N* (%)[d]				0.62
R0	56 (86.2)	55 (90.2)	–4.01 (–15.25 to 7.23)	
R1	9 (13.8)	6 (9.8)		
No. retrieved lymph nodes, mean (SD)	18.2 (9.0)	16.2 (8.4)	1.68 (–1.22 to 4.58)	0.07
With malignancies	19.7 (8.9)	18.4 (8.7)	1.27 (–1.81 to 4.36)	0.41
Patients of complication, *N* (%)	37 (31.9)	42 (35.3)	–3.40 (–15.47 to 8.67)	0.58
No. complications, *N* (%)	42	50		
Clinically relevant postoperative pancreatic fistula	13 (11.2)	14 (11.8)		0.89
Delayed gastric emptying	4 (3.4)	8 (6.7)		0.25
Post-pancreatectomy hemorrhage	3 (2.5)	3 (2.5)		0.57
Others	22 (18.9)	25 (21.0)		0.87
Severe complication (grade IIIa or more), *N* (%)[e]	18 (15.5)	18 (15.1)	0.39 (–8.82 to 9.60)	0.42
In hospital mortality, *N* (%)	0	0		
90-day mortality, *N* (%)	0	0		
60-day readmission, *N* (%)	15 (12.9)	16 (13.4)	–0.51 (–9.17 to 8.14)	0.90

[a]Plus–minus values are means ± standard deviation. The results are shown for modified intention-to-treat group, which included patients who underwent surgery after randomization.
[b]Treatment Effect (effect size) was expressed mean difference in continuous data and risk difference in case of proportional data on primary and secondary outcomes.
[c]Functional recovery was statistically different between open and laparoscopic group ($P=0.03$). The *P* value for the first assessment of the primary end point is from a Fine-Gray model.
[d]The extent of resection was defined by dividing it into two categories. R0 resection; microscopic margin-negative resection and R1 resection; microscopically margin-positive resection.
[e]Adverse events were classified according to the Clavien–Dindo system and described in Table S4, Supplemental Digital Content 4, http://links.lww.com/JS9/D346.

pancreatoduodenectomy for periampullary tumors is supported by retrospective studies and randomized studies in terms of the number of retrieved lymph nodes and curative resection rates[15,16], although survival outcomes have not yet been fully evaluated. Our study showed similar results between the two groups in terms of the number of retrieved lymph nodes and curative resection and short-term survival rates.

Many studies have reported that laparoscopic surgery minimizes the inflammatory reaction compared to open surgery, as reflected in cytokine levels. Similar measurements have been performed in previous studies. A meta-analysis of patients with colorectal cancer showed lower postoperative cytokine elevations in the laparoscopic group compared to the open group[31]. However, one study on pancreaticoduodenectomy reported similar cytokine elevations in both the laparoscopic and open surgery groups[30]. Consistent with these previous findings, our study did not observe significant differences in the magnitude of cytokine elevation between the laparoscopic and open surgery groups.

We did not observe any statistically significant changes in any QoL component between the two groups. This may be due to the timing of our measurements, as another study reported improvements in QoL following laparoscopic surgery when assessed at an intermediate time point. It's possible that QoL differences might emerge after a longer period, such as six months. To address this limitation, we plan to measure QoL in a future study over a longer timeframe.

This trial has some major limitations. First, it excluded patients with high surgical risk profiles, such as those with malignant disease involving major vascular invasion, a high ASA score, an ECOG status greater than 3, defined as capable of only limited self-care or confined to bed or chair more than 50% of waking hours, which is hard to perform the clinical study, and severe obesity in oriental criteria (BMI over 30). These factors are likely to occur in real-world clinical settings but were excluded due to safety concerns reported in recent randomized studies. While this approach may result in favorable postoperative complications, its general applicability to laparoscopic pancreaticoduodenectomy might be limited by this exclusion. The findings of this study should be interpreted within the context of the specified inclusion criteria. Second, unlike the LEOPARD-2 trial[15], we did not blind the study participants, including patients and surgeons following the recommendation of the safety board. We enhanced objectivity by using data measurements conducted by medical personnel not involved in the study; nonetheless, the lack of blinding in the study results could compromise objectivity. Third, the advantage of laparoscopic pancreatoduodenectomy may not apply to surgeons in smaller centers. Future studies should evaluate this approach in a prospectively maintained database across all centers for long-term follow-up, as recommended by the IDEAL framework (Idea, Development, Exploration, Assessment, Long-term follow-up) and the Miami International Guidelines[38,39]. Effective training and educational efforts are essential to shorten the learning curve and promote the widespread adoption of laparoscopic pancreatoduodenectomy. Fourth, the study population for each type of cancer was heterogeneous, with small subgroup sizes, and the follow-up time was short. Prospective, long-term studies are needed to confirm

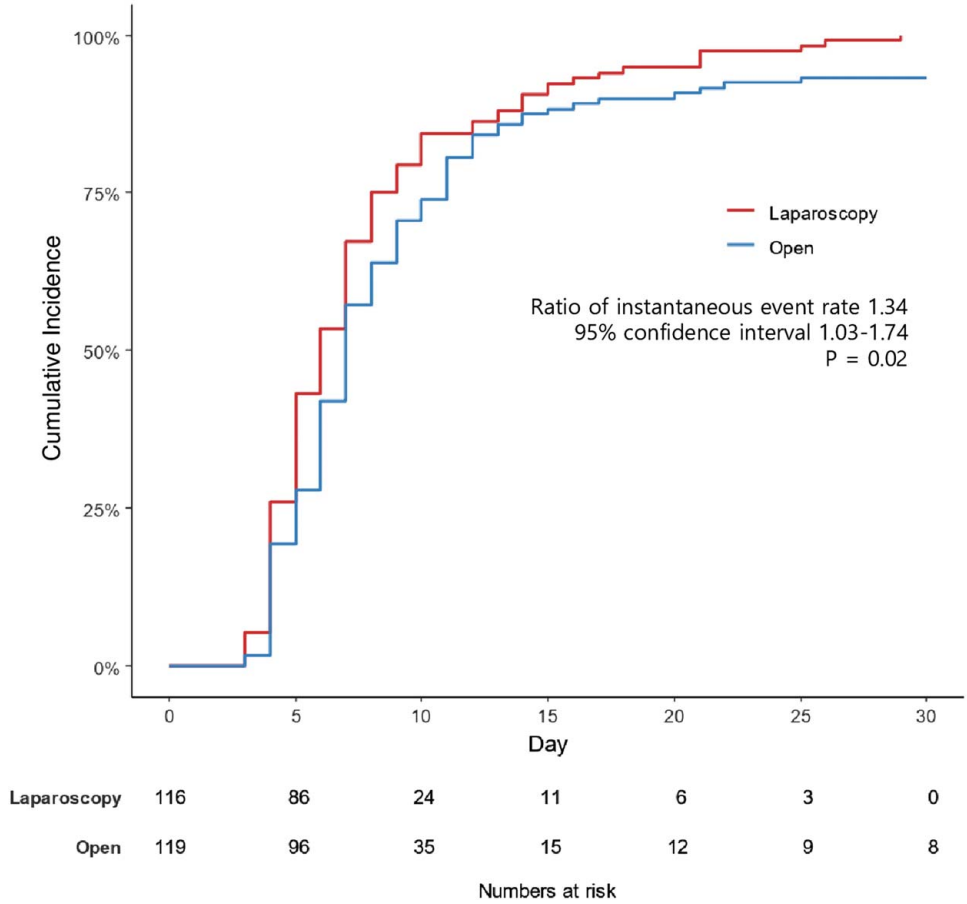

Figure 2. Primary end point for cumulative incidence of functional recovery after surgery. Shown are the cumulative incidence curves and Fine-Gray model for achievement of functional recovery 30 days after surgery between laparoscopic and open pancreatoduodenectomy groups. Functional recovery comprised of five domains including pain control, restored mobility, caloric intake, infection, and fluid administration, and achievement of functional recovery was defined as first day of 3 or more consecutive achievement of all domains.

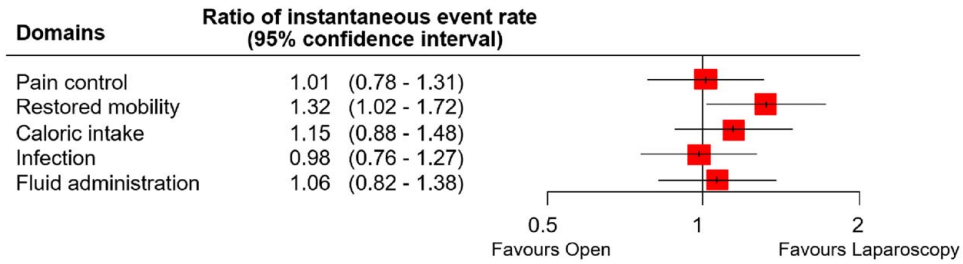

Figure 3. Forest plot for achievement of five domains for functional recovery. Red square of the first line represents point estimates for the instantaneous ratio of functional recovery in patients who underwent laparoscopic pancreatoduodenectomy as compared to patients who underwent open pancreatoduodenectomy. Horizontal lines indicate the associated 95% confidence intervals. Each line indicates five domains which were included functional recovery such as pain control, restored mobility, caloric intake, infection, fluid administration. Especially, restored mobility showed faster in laparoscopic pancreatoduodenectomy group than open group significantly.

the oncological safety of laparoscopic pancreatoduodenectomy. Lastly, to ensure study homogeneity, cases of robotic pancreatoduodenectomy were not included. However, considering that robotic surgery may represent the future of minimally invasive surgery, a comparative study among these modalities should be pursued.

Conclusions

Laparoscopic pancreatoduodenectomy demonstrated a modest reduction in the time to functional recovery compared to open surgery for selected patients under the care of experienced surgeons. However, the overall clinical benefit of the procedure

remains uncertain due to study limitation and similar outcomes observed between the laparoscopic and open surgery groups for other outcome parameters. Future studies are necessary to demonstrate the potential advantages of laparoscopic pancreatoduodenectomy and to identify the patient population that can benefit from this intervention.

Ethical approval

This study was approved by the Institutional Review Board (IRB No. 2018-0687) in Asan medical center.

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Author contribution

Y.-S.Y.: concept, design, drafting the article. W.L.: concept, design, drafting the article. C.M.K.: concept, design, drafting the article. T.H.; concept, design, revising manuscript.S.H.S.: drafting / revising manuscript.J.W.L.: acquisition of data, analysis of data. D.W.H.: acquisition of data, analysis of data. K.B.S.: acquisition of data, analysis of data. J.W.K.: acquisition of data, analysis of data.M.K.S.: revising manuscript. K.S.: acquisition of data, analysis of data. J.B.L.: acquisition of data, analysis of data. S.C.K.: concept, design, revising the article.

Conflicts of interest disclosure

The authors have no related conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: clinicaltrials.gov.
2. Unique Identifying number or registration ID: NCT03870698.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.clinicaltrials.gov/study/NCT03870698?cond=NCT03870698&rank=1.

Guarantor

Song Cheol Kim.

Data availability statement

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, please send an e-mail to the following address: drksc@amc.seoul.kr.

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