OXFORD

BJS, 2021, **108**, 1043–1049
DOI: 10.1093/bjs/znab295
Advance Access Publication Date: 6 September 2021
Randomized Clinical Trial

Short-term outcomes of a multicentre randomized clinical trial comparing laparoscopic pylorus-preserving gastrectomy with laparoscopic distal gastrectomy for gastric cancer (the KLASS-04 trial)

D. J. Park[1,2], Y.-W. Kim[3], H.-K. Yang [1], K. W. Ryu [3], S.-U. Han[4], H.-H. Kim [2], W.-J. Hyung [5], J. H. Park [6], Y.-S. Suh[1,2], O. K. Kwon[7], H. M. Yoon[3], W. Kim[8], Y.-K. Park[9], S.-H Kong[1], S. H. Ahn [2] and H.-J. Lee [1,*]

[1]Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea
[2]Department of Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Surgery, National Cancer Centre, Goyang, Korea
[4]Department of Surgery, Ajou University Hospital, Suwon, Korea
[5]Department of Surgery, Yonsei University Severance Hospital, Seoul, Korea
[6]Department of Surgery, Gyeongsang National University Hospital, Daegu, Korea
[7]Department of Surgery, Kyungpook National University Hospital, Daegu, Korea
[8]Department of Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
[9]Department of Surgery, Chonnam National University Medical School, Hwasun, Korea

*Correspondence to: Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine, 101, Daehak-ro Jongno-gu, Seoul 03080, Korea (e-mail: appe98@snu.ac.kr)

Abstract

Background: There remain concerns about the safety and functional benefit of laparoscopic pylorus-preserving gastrectomy (LPPG) compared with laparoscopic distal gastrectomy (LDG). This study evaluated short-term outcomes of a randomized clinical trial (RCT) comparing LPPG with LDG for gastric cancer.

Methods: The Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS)-04 trial was an investigator-initiated, open-label, parallel-assigned, superiority, multicentre RCT in Korea. Patients with cT1N0M0 cancer located in the middle third of the stomach at least 5 cm from the pylorus were randomized to undergo LPPG or LDG. Participants, care givers and those assessing the outcomes were not blinded to group assignment. Outcomes were 30-day postoperative morbidity rate and death at 90 days.

Results: Some 256 patients from nine institutions were randomized (LPPG 129 patients, LDG 127 patients) between July 2015 and July 2017 and outcomes for 253 patients were analysed. Postoperative complications within 30 days were seen in 19.3 and 15.5 per cent in the LPPG and LDG groups respectively ($P = 0{\cdot}419$). Postoperative pyloric stenosis was observed in nine (7.2 per cent) and two (1·5 per cent) patients in the LPPG and LDG groups ($P = 0{\cdot}026$) respectively. In multivariable analysis higher BMI was a risk factor for postoperative complications (odds ratio 1·17, 95 per cent c.i. 1·04 to 1·32; $P = 0{\cdot}011$). Death at 90 days was zero in both groups.

Conclusion: Postoperative complications and mortality was comparable in patients undergoing LPPG and LDG. Registration number: NCT02595086 (http://www.clinicaltrials.gov).

Introduction

Laparoscopic distal gastrectomy (LDG) with lymph node dissection was first reported by Kitano in 1994[1]. Laparoscopic gastrectomy is now a standard treatment for early gastric cancer (EGC) as it is safe and effective as demonstrated in RCTs from Korea[2,3]. As 95 per cent of patients achieve long-term survival without recurrence after gastrectomy for early cancer, more focus in the surgical community is on sustaining quality of life (QoL) of the patient after gastrectomy. Surgery aimed at preserving organ function, such as laparoscopic pylorus-preserving gastrectomy (LPPG), for EGC may reduce post-gastrectomy symptoms by preserving some aspects of gastrointestinal function[4–6]. Although pylorus-preserving gastrectomy (PPG) was initially used for peptic ulcer treatment, it is now employed for EGC in Korea and Japan[7]. LPPG is considered oncologically safe because EGC located in the middle third of the stomach and more than 5 cm from the pylorus has a very low risk for metastasis to the suprapyloric lymph nodes[8].

LPPG is associated with reduced weight loss and a lower risk for dumping syndrome, cholelithiasis and reflux gastritis compared with distal gastrectomy. This may be due to preservation of the hepatic and pyloric branches of the vagal nerve[9,10]. However, a multicentre randomized controlled trial (RCT) has not yet been performed. The aim of the Korean Laparoendoscopic

Received: February 21, 2021. **Revised:** April 20, 2021. **Accepted:** July 14, 2021

Gastrointestinal Surgery Study (KLASS)-04 trial was to evaluate functional benefits, oncological outcome and safety of LPPG. The short-term outcomes of LPPG and LDG are reported in the present study.

Methods

Study design

This was an investigator-initiated, randomized, controlled, parallel group and superiority trial comparing LPPG with LDG for middle-third cT1N0M0 gastric cancer (registration number: NCT02595086 (http://www.clinicaltrials.gov)). The study was approved by the institutional review board (IRB) (IRB No. H-1502–058-648) of Seoul National University Hospital, followed by each investigator's IRB. All researchers conducted this study in compliance with the Declaration of Helsinki. All patients provided written informed consent to participate in the study prior to enrolment. This RCT was monitored by an independent data and safety monitoring committee operated by the Medical Research Collaborating Centre (MRCC) of Seoul National University Hospital.

Participants

Inclusion criteria were age 20–80 years, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, pathologically proven gastric adenocarcinoma[11], cT1N0M0 disease stage according to the American Joint Committee on Cancer/Union for International Cancer Control 7th edition[12], tumour located in the middle third of the stomach and at least 5 cm from the pylorus and able to be be resected by distal gastrectomy, which means the proximal margin was at least 4–5 cm from the gastro-oesophageal junction.

Patients with a history of other cancers, synchronous EGC or adenoma of the antrum and previous gastric surgery including gastrojejunostomy were excluded. Cancer staging was performed with gastroscopy, endoscopic ultrasonography and CT.

Quality control

For surgical quality control, the surgeon should have performed more than 50 cases of LDG and open distal gastrectomy. The institutional volume was set at a minimum of 80 gastric cancer resections per year. At least one unedited LPPG video with extracorporeal gastrogastrostomy was submitted by surgeons who fulfilled the criteria. The video was reviewed, using a standardized evaluation sheet, by two or more reviewers with experience in LPPG, who were blinded to the name of the institution. The review was conducted to determine the competence of the surgeons. Lymph node dissection, infrapyloric vessel preservation, hepatic nerve preservation, gastrogastrostomy and general skill were assessed and scored.

Randomization

Patient data were entered into a web-based electrical clinical report form managed by the MRCC of the Seoul National University. Randomization was performed intraoperatively immediately after diagnostic laparoscopy and the patient was allocated to LPPG or LDG. If unexpected distant metastasis or an adjacent organ invasion was detected at laparoscopy, the randomization was not conducted and the patient was recorded as 'screening failure'. Randomization was with a 1 : 1 ratio with each surgeon as a stratification factor. The block randomization method with mixed block sizes of 2 and 4 within each stratum was performed using SAS® version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) through online randomization managed by the MRCC of Seoul National University.

Surgical procedures

Laparoscopic pylorus-preserving gastrectomy

After partial omentectomy, station 6 lymph nodes were dissected meticulously to preserve the infrapyloric vessels. Station 5 lymph node dissection was not performed, and the right gastric arcade was ligated 3 cm from the pylorus. After lymph node dissection and mobilization of the stomach, the stomach was extracted through a mini-laparotomy. The stomach was transected, and a handsewn end-to-end gastrogastrostomy was performed. The variations of infrapyloric artery anatomy, vascular damage, hepatic branch of vagus nerve preservation, and antrum cuff length were recorded.

Laparoscopic distal gastrectomy

LDG was performed using one of the following reconstruction methods: gastroduodenostomy (Billroth I), gastrojejunostomy (Billroth II) with or without Braun jejunojejunostomy, and Roux-en-Y gastrojejunostomy. Both intracorporeal and extracorporeal anastomoses were accepted.

It was mandatory to check the pathology of intraoperative frozen sections of the proximal and distal margins in both groups.

Follow-up

The patients enrolled in both groups were followed up 1 month after discharge, and then at 6-month intervals for 3 years. At every follow-up, physical examination, blood tests, including a complete blood count, liver-function test, nutrition markers (total protein, albumin and transferrin) and tumour markers, were performed. Gastroscopy was performed every year, and abdominal sonography and abdominal CT were performed alternately every 6 months.

Endpoints

The primary endpoint of the KLASS-04 study was incidence of dumping syndrome according to the Sigstad score (7 or greater) at 1 year after surgery[13]. A power calculation revealed that 128 patients in each group had to be included to demonstrate a statistically significant reduction in dumping after LPPG.

Secondary endpoints were 30-day operative morbidity rate and 90-day mortality rate and this is reported in the present study[13]. All patients were followed for 3 years after surgery. Early complications were defined as surgery-related complications that occurred within postoperative day (POD) 30. Surgery-related complications after POD 30 were defined as late complications. Complications were graded according to the Clavien–Dindo classification[14]. Complications included wound complications, fluid collection/abscess, intra-abdominal bleeding, intraluminal bleeding, ileus, anastomotic or pyloric stenosis, leakage, pancreatitis/pancreatic fistula, and pulmonary, urinary, renal, hepatic, cardiac, endocrine or miscellaneous complications. They were defined and categorized according to the KLASS-02 study[15]. Postoperative stenosis consists of pyloric stenosis and anastomosis stenosis. Pyloric stenosis was defined as delayed gastric emptying, which required balloon dilatation or stent insertion. Anastomosis stenosis was defined as a stricture at gastrogastrostomy in gastroscopy.

Statistical analysis

All patients were included in the intention-to-treat (ITT) group. The actual treatment group included patients who swapped to

the other surgical approach (LPPG *versus* LDG) after randomization, excluding patients who underwent total gastrectomy. To investigate the difference in proportions of patients between the two groups, a χ^2 test or Fisher's exact test was applied. Continuous variables were analysed using an independent *t*-test or Wilcoxon rank sum test. Logistic regression analysis was applied to evaluate risk factors affecting morbidity. A stepwise method was applied to select multiple regression models. Variables with $P < 0.200$ after univariable analysis were considered for the stepwise process. $P < 0.050$ was considered statistically significant. Statistical analysis was conducted using SAS® version 9·4.

Results

Patients

From July 2015 to July 2017, 256 patients were enrolled from nine institutions and randomized to LPPG (129 patients) or LDG (127 patients) (*Fig. 1*). These numbers were used for the ITT analysis. The per protocol analysis included 124 patients that underwent LPPG and 129 patients after LDG. There were no statistically significant differences in patient demographics or tumour characteristics between the two groups (*Table 1*).

Operative details

The mean operation time was longer for the LPPG group than that for the LDG group (193·6 *versus* 180·9 min, $P = 0·007$) (*Table 2*). Hepatic and coeliac branches of the vagal nerve were preserved in 96·8 and 25·0 per cent of patients in the LPPG and LDG group respectively (*Table 2*).

Morbidity and mortality rates

In ITT analysis, the percentage of patients with early postoperative complications was 19·3 per cent in the LPPG group and 15·5 per cent in the LDG group ($P = 0·419$) (*Table 3*; supplementary material online, *Table S1*). Postoperative stenosis of the anastomosis or pylorus occurred in eight patients (6·2 per cent) in the LPPG group and in three (2·4 per cent) patients in the LDG group ($P = 0·129$). When pyloric stenosis was excluded, the complication rates for LPPG and LDG were 13·1 and 16·5 per cent respectively. Grade III or higher complications according to Clavien–Dindo classification occurred in 9·3 per cent of patients in the LPPG group and 7·1 per cent in the LDG group ($P > 0.050$). Two patients underwent reoperations in the LDG group because of intra-abdominal bleeding and stenosis of the anastomosis.

The per protocol analysis showed outcomes comparable with the ITT analysis for early complications, except for stenosis. Postoperative stenosis of the anastomosis or pylorus occurred in nine (7·3 per cent) of 124 LPPG patients and two (1·6 per cent) of 129 LDG patients ($P = 0·026$). Of the 11 patients with stenosis, one patient had conservative management, seven underwent balloon dilatation, two underwent stent insertion and one patient underwent revision of the jejunojejunostomy.

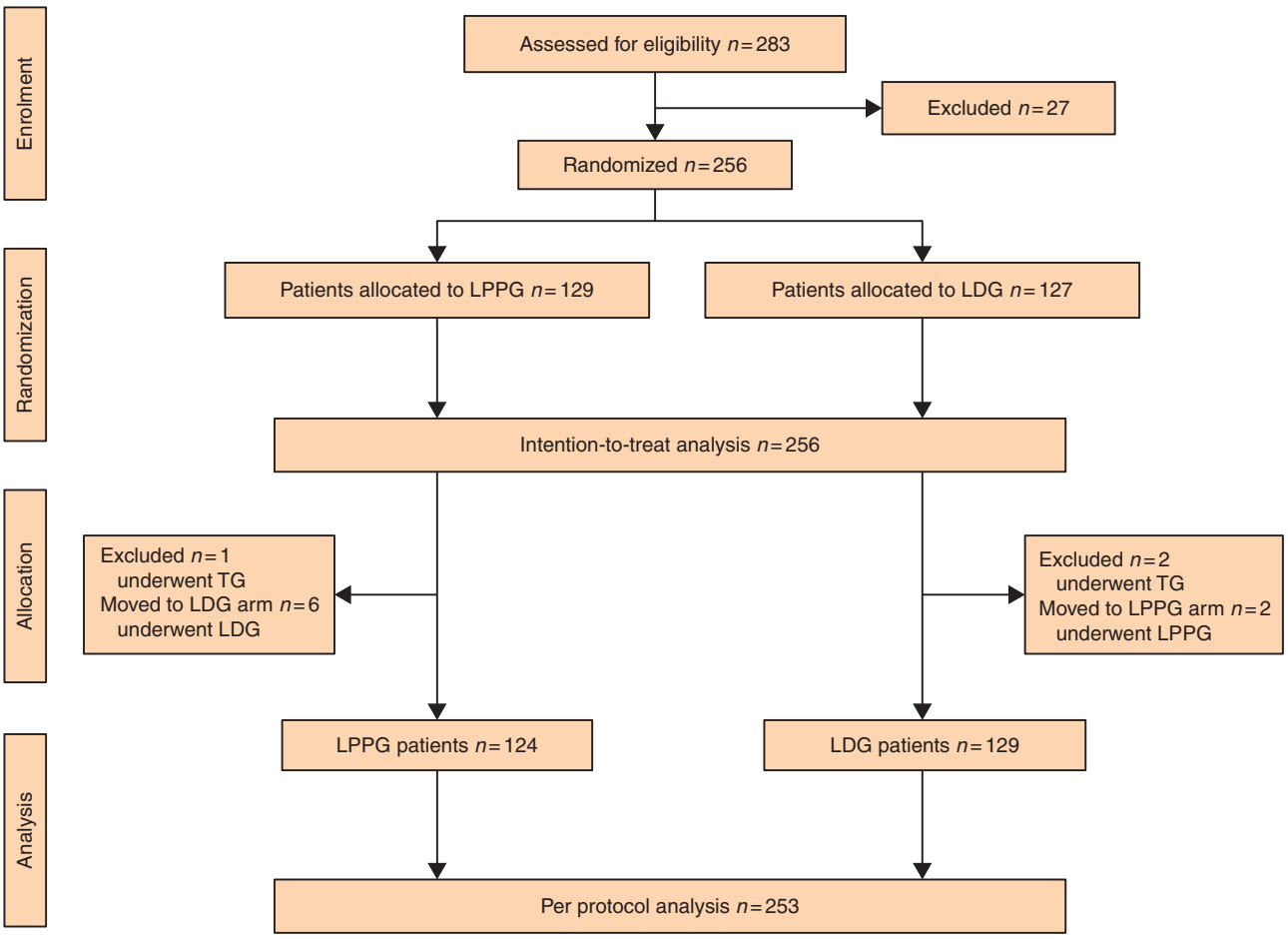

Fig. 1 CONSORT diagram

LPPG, laparoscopic pylorus-preserving gastrectomy; LDG, laparoscopic distal gastrectomy; TG, total gastrectomy

Table 1 Patient and tumour characteristics

Characteristic	Intention to treat			Per protocol		
	LPPG (*n* = 129)	LDG (*n* = 127)	P	LPPG (*n* = 124)	LDG (*n* = 129)	P
Sex (M : F)	63 : 66	63 : 64	0.902	58 : 66	67 : 62	0.411
Age (years)*	56.0(10.6)	57.7(10.4)	0.186	55.6(10.6)	58.1(10.2)	0.060
BMI (kg/m^2)*	23.5(2.6)	23.7(2.8)	0.809	23.5(2.6)	23.7(2.8)	0.843
ASA grade						
1	77 (59.7)	79 (62.2)	0.188	76 (61.3)	78 (60.5)	0.362
2	52 (40.3)	45 (35.4)		48 (38.7)	48 (37.2)	
3	0 (0)	3 (2.4)		0 (0)	3 (2.3)	
ECOG						
0	123 (95.4)	123 (96.9)	0.749	119 (96.0)	124 (96.1)	0.999
1	6 (4.6)	4 (3.1)		5 (4.0)	5 (3.9)	
Co-morbidity						
Hypertension	33 (25.6)	36 (28.4)	0.618	32 (25.8)	36 (27.9)	0.706
Diabetes mellitus	11 (8.5)	18 (14.2)	0.154	10 (8.1)	18 (13.9)	0.135
Previous abdominal operation	34 (26.4)	28 (22.1)	0.421	34 (27.4)	27 (20.9)	0.228
Tumour location						
Lesser curvature	28 (21.7)	40 (31.5)	0.295	28 (22.6)	40 (31.0)	0.417
Greater curvature	50 (38.8)	41 (32.3)		49 (39.5)	41 (31.8)	
Anterior wall	22 (17.0)	23 (18.1)		21 (16.9)	23 (17.8)	
Posterior wall	29 (22.5)	23 (18.1)		26 (21.0)	25 (19.4)	
Tumour site						
Upper body	2 (1.6)	1 (0.8)	0.725	2 (1.6)	1 (0.8)	0.536
Mid body	104 (80.6)	100 (78.7)		101 (81.4)	100 (77.5)	
Lower body	23 (17.8)	26 (20.5)		21 (16.9)	28 (21.7)	
cT stage						
cT1a	42 (32.6)	44 (34.6)	1.000	41 (33.1)	44 (34.1)	0.966
cT1b	69 (53.5)	71 (55.9)		65 (52.4)	73 (56.6)	
cN stage						
cN0	129 (100.0)	127 (100.0)	1.000	124 (100.0)	129 (100.0)	1.000

Values in parentheses are percentages unless indicated otherwise; Chi-square test or Fisher's exact test was used for categorical variables, and independent t-test or Wilcoxon rank sum test was used for continuous variables.*Values are mean(s.d.). M, male; F, female; LPPG, laparoscopic pylorus-preserving gastrectomy; LDG, laparoscopic distal gastrectomy; ECOG, Eastern Cooperative Oncology Group performance status.

BMI was the only statistically significant independent risk factor for early complications in multivariable analysis (odds ratio 1·17, 95 per cent c.i. 1·04 to 1·32; $P = 0·011$) (supplementary material online, *Table S2*). BMI was also the risk factor for postoperative pyloric stenosis (supplementary material online, *Table S3*).

There was no significant difference in readmission rate at 30 days (2·4 per cent in LPPG and 3·1 per cent in LDG, $P > 0·999$) and reoperation rate at 90 days after surgery (0 per cent in LPPG and 1·6 per cent in LDG, $P = 0·498$). No patient died within 90 days after the operation.

Pathology

The mean(s.d.) number of resected lymph nodes was 38.1(14.4) in the LPPG group and 45.2(20.9) in the LDG group ($P = 0·005$). Tumour size, lymphatic invasion, vascular invasion, histology, pT, pN and stage were comparable for the two groups (*Table 4*). The distance between the tumour and the proximal resection margin was larger in LDG group than that in the LPPG group (3·5 *versus* 2·7 cm, $P = 0·004$). The number of examined station 6 lymph nodes was similar between LPPG and LDG (6·1 *versus* 6·6, $P = 0·263$). There were no metastases in the station 5 lymph nodes of the LDG group (supplementary material online, *Table S4*).

Discussion

This study showed that the incidence of early complications 30 days after surgery was 19·3 per cent in the LPPG group and 15·5 per cent in the LDG group. The complication rate after LDG was 13·0 per cent in the KLASS 01 trial[3]. This difference between the two trials was the proportion of patients with middle-third cancers (100 per cent in KLASS 04 and 31·1 per cent in KLASS 01). LDG is considered to be more difficult for middle-third gastric cancer than for lower-third cancer and this may explain the slightly higher complication rate in the present study. For LPPG, retrospective studies show an overall complication rate between 14·7 and 17·3 per cent[16,17]. The present multicentre study showed that the complications of LPPG were even higher (19·3 per cent). Considering that a more meticulous dissection is required to preserve the infrapyloric artery and the operation time was about 10 minutes longer, it suggests that LPPG is a more difficult operation. Gastric stasis or outlet obstruction is the most frequent complication, ranging from 6·2 to 7·8 per cent[16–18]. The present study showed a 6.5 per cent rate of pyloric stenosis, but all patients recovered well without reoperation.

Hiki and colleagues also reported that BMI and surgical experience with LPPG were identified as risk factors for postoperative complications[16]. BMI was the only risk factor of postoperative pyloric stenosis in the present study and preservation of the hepatic branch and infrapyloric artery was not. The reason why preservation of both structures was not statistically significant in the present study may be the small number of patients in the study.

Tanaka and co-workers compared LPPG with open PPG and showed that the incidence of gastric stasis was 6·7 per cent in the LPPG group and 5·6 per cent in the PPG group[19]. In the present study, 6·5 per cent of the LPPG group had pyloric stenosis, somewhat higher than that after open PPG in the Tanaka's study. An explanation might be the use of ultrasonically activated shears leading to thermal spread in laparoscopic surgery[20]. It is hypothesized that residual heat due to increased temperature of the instrument after energy activation may cause thermal injury to the

Table 2 Operative details

Detail	Intention to treat			Per protocol		
	LPPG (*n* = 129)	LDG (*n* = 127)	P	LPPG (*n* = 124)	LDG (*n* = 129)	P
Operation type			<0.001			<0.001
Pylorus-preserving gastrectomy	122 (94.6)	2 (1.6)		124 (100)	0	
Distal gastrectomy	6 (4.7)	123 (96.9)		0	129 (100)	
Total gastrectomy	1 (0.7)	2 (1.5)		0	0	
Operation time (min)*	194.5(40.5)	180.9(46.1)	0.005	193.6(39.2)	180.9(45.1)	0.007
Blood loss (ml)*	58.6(80.6)	51.6(55.2)	0.519	58.6(81.6)	51.9(55.4)	0.528
Transfusion (ml)*	0.8(8.8)	0	0.325	0.8(9.0)	0	0.311
Lymph node dissection			0.809			0.367
D1+	128 (99.2)	125 (98.4)		124 (100.0)	127 (98.4)	
D2	1 (0.8)	2 (1.6)		0	2 (1.6)	
Anastomosis			<0.001			<0.001
Gastrogastrostomy	122 (94.6)	2 (1.6)		124 (100)	0	
Gastroduodenostomy (Billroth I)	2 (1.5)	60 (47.2)		0	59 (45.7)	
Gastrojejunostomy (Billroth II)	3 (2.3)	41 (32.3)		0	43 (33.3)	
Gastrojejunostomy (Roux-en-Y)	1 (0.8)	22 (17.)		0	27 (21.0)	
Oesophagojejunostomy	1 (0.8)	2 (1.6%)		0	0	
Creation of anastomosis			<0.001			<0.001
Extracorporeal	123 (95.4)	43 (33.9)		123 (99.2)	44 (34.1)	
Intracorporeal	6 (4.6)	84 (66.1)		1 (0.8)	85 (65.9)	
Method of anastomosis			<0.001			<0.001
Hand-sewing	116 (89.9)	2 (1.6)		118 (95.2)	0	
Stapler	13 (10.1)	125 (98.4)		6 (4.8)	129 (100)	
Incision length (cm)*	5.4(1.0)	4.7(1.5)	<0.001	5.4(1.0)	4.8(1.5)	0.005
Distance between tumour and pylorus (cm)*	8.4(3.2)	8.5(2.7)	0.181	8.4(3.2)	8.5(2.7)	0.312
Preservation of hepatic branch of vagal nerve	105 (81.4)	18 (14.2)	<0.001	101 (81.5)	22 (17.1)	<0.001
Preservation of coeliac branch of vagal nerve	31 (24.0)	8 (6.3)	0.041	31 (25.0)	8 (6.2)	0.001
Injury to infrapyloric artery	3 (2.3)	NA		1 (0.8)	NA	
Injury to infrapyloric vein	6 (4.7)	NA		4 (3.2)	NA	
Antral cuff (cm)*	4.1(0.9)	NA		4.1(0.9)	NA	

Values in parentheses are percentages unless indicated otherwise; Chi-square test or Fisher's exact test was used for categorical variables, and independent t-test or Wilcoxon rank sum test was used for continuous variables.*Values are mean(s.d.). LDG, laparoscopic distal gastrectomy; LPPG, laparoscopic pylorus-preserving gastrectomy; NA, not applicable.

Table 3 Morbidity and mortality

	Intention to treat			Per protocol		
	LPPG (*n* = 129)	LDG (*n* = 127)	P	LPPG (*n* = 124)	LDG (*n* = 129)	P
Overall morbidity	23 (17.8)	21 (16.5)	0.784	24 (19.3)	20 (15.5)	0.419
Wound infection	6 (4.7)	3 (2.4)	0.500	6 (4.8)	3 (2.3)	0.327
Fluid collection/abscess	2 (1.6)	2 (1.6)	1.000	2 (1.6)	2 (1.6)	1.000
Intra-abdominal bleeding	0 (0.0)	2 (1.6)	0.245	0 (0.0)	2 (1.6)	0.498
Intraluminal bleeding	2 (1.6)	1 (0.8)	1.000	2 (1.6)	1 (0.8)	0.616
Ileus	0 (0.0)	3 (2.4)	0.121	0 (0.0)	3 (2.3)	0.247
Stenosis	8 (6.2)	3 (2.4)	0.129	9 (7.3)	2 (1.6)	0.026
Pylorus	7 (5.4)	1 (0.8)	0.014	8 (6.5)	0 (0.0)	0.003
Anastomosis	1 (0.8)	2 (1.6)	>0.999	1 (0.8)	2 (1.6)	0.490
Anastomotic leak	2 (1.6)	2 (1.6)	1.000	2 (1.6)	2 (1.5)	1.000
Pancreatitis	0 (0.0)	1 (0.8)	0.496	0 (0.0)	1 (0.8)	1.000
Pulmonary	1 (0.8)	3 (2.4)	0.368	1 (0.8)	3 (2.3)	0.622
Cardiac	0 (0.0)	1 (0.8)	0.496	0 (0.0)	1 (0.8)	1.000
Others	5 (3.9)	1 (0.8)	0.213	5 (4.0)	1 (0.8)	0.114
Grade of complications†						
I	9 (7.0)	8 (6.3)	0.828	9 (7.3)	8 (6.2)	0.737
II	8 (6.2)	6 (4.7)	0.603	8 (6.4)	6 (4.7)	0.531
IIIa	12 (9.3)	7 (5.5)	0.247	13 (10.5)	6 (4.7)	0.078
IIIb	0 (0.0)	2 (1.6)	0.245	0 (0.0)	2 (1.6)	0.498
Complications except pyloric stenosis (DGE)	16 (13.1)	21 (16.5)	0.448	16 (13.8)	20 (15.5)	0.706
Deaths at 90 days	0	0	1.000	0	0	1.000

Values in parentheses are percentages. Chi-squared test or Fisher's exact test was used.†Clavien–Dindo classification. LPPG, laparoscopic pylorus-preserving gastrectomy; LDG, laparoscopic distal gastrectomy; DGE, delayed gastric emptying.

Table 4 Pathology

Characteristic	Intention to treat			Per protocol		
	LPPG (*n* = 129)	LDG (*n* = 127)	P	LPPG (*n* = 124)	LDG (*n* = 129)	P
Tumour size (cm)*	2.3(15.2)	2.5(1.7)	0.220	22.4(14.09)	24.6(16.1)	0.311
Retrieved lymph nodes*	38.1(14.4)	45.2(20.9)	0.005	37.8(14.1)	44.9(20.7)	0.005
Proximal resection margin (cm)*	2.7(1.8)	3.5(2.4)	0.004	2.7(1.9)	3.4(2.4)	0.007
Distal resection margin (cm)*	3.9(2.8)	8.1(2.7)	<0.001	3.6(2.6)	8.1(2.7)	<0.001
Lymphatic invasion (+)	10 (7.7)	14 (11.0)	0.339	9 (7.3)	15 (11.6)	0.288
Vascular invasion (+)	4 (3.1)	3 (2.4)	0.860	4 (3.2)	2 (1.6)	0.436
Histology						
Differentiated	34 (26.4)	36 (28.3)	0.580	21 (25.0)	38 (29.4)	0.414
Undifferentiated	75 (58.1)	75 (59.1)		67 (54.0)	74 (57.3)	
Others	20 (15.5)	16 (12.6)		25 (20.2)	17 (13.2)	
pT stage			0.652			0.662
T1a	79 (61.2)	74 (58.3)		75 (60.5)	78 (60.5)	
T1b	43 (33.3)	40 (31.5)		42 (33.9)	40 (31.0)	
T2	4 (3.1)	8 (6.3)		4 (3.2)	7 (5.4)	
T3	2 (1.6)	3 (2.4)		1 (0.8)	3 (2.3)	
T4a	0 (0)	1 (0.8)		0 (0.0)	1 (0.8)	
pN stage			0.451			0.220
N0	115 (89.2)	116 (91.3)		110 (88.7)	118 (91.5)	
N1	10 (7.7)	4 (3.2)		10 (8.1)	4 (3.1)	
N2	3 (2.3)	4 (3.2)		2 (1.6)	5 (3.9)	
N3a	0 (0)	1 (0.8)		0 (0.0)	1 (0.8)	
N3b	1 (0.8)	1 (0.8)		1 (0.8)	1 (0.8)	
Distant metastasis	0	0				
pTNM stage			0.121			0.058
IA	111 (86.0)	108 (85.0)		106 (85.5)	112 (86.8)	
IB	14 (10.8)	7 (5.5)		14 (11.3)	6 (4.6)	
IIA	2 (1.6)	8 (6.3)		2 (1.6)	7 (5.4)	
IIB	1 (0.8)	2 (1.6)		1 (0.8)	2 (1.6)	
IIIA	1 (0.8)	1 (0.8)		0 (0.0)	2 (1.6)	

Chi-squared test or Fisher's exact test was used for categorical variables, and independent t-test or Wilcoxon rank sum test was used for continuous variables. LPPG, laparoscopic pylorus-preserving gastrectomy; LDG, laparoscopic distal gastrectomy.

pylorus, which results in temporary dysfunction of the pylorus and pyloric stenosis. Because the temperature could be higher in obese patients with high fat content, a higher BMI was a risk factor for pyloric stenosis after LPPG.

Kodera and colleagues[21] evaluated lymph node yield in 491 patients with cancers in the middle third of the stomach and found that metastases of nodal station 5 in patients with EGC was less than 5 per cent. Kong and co-workers[8] also assessed metastasis to station 5 lymph nodes for cancers with a distal margin of less than 6 cm. In patients with T1b cancers, this was 2·7 per cent. Because there was no metastasis in the station 5 lymph nodes in the LDG group in the present study, LPPG leaving station 5 lymph nodes *in situ* seems safe for middle-third EGC.

One limitation of the present study was that the anastomosis for LPPG was mostly performed extracorporeally through a mini-laparotomy wound. There have been some reports of higher rates of gastric stasis (10 per cent) in patients that underwent an intracorporeal gastrogastrostomy[22]. Hence for this study, extracorporeal anastomosis was performed using an end-to-end hand-sewing technique. Despite the wound, this allowed the surgeons to palpate the margin before transection of the stomach. In the present study, although the wound was longer in the LPPG group than that in the LDG group, the proximal margin length was higher in LPPG. Once the benefits of laparoscopy-assisted PPG are established, techniques in intracorporeal anastomosis can be further optimized for totally laparoscopic PPG.

When comparing the clinical outcome of PPG and conventional distal gastrectomy with gastroduodenostomy reported by Park and colleagues[10], postprandial symptoms, bile regurgitation and gallstones were less frequent in patients that underwent PPG than those that underwent distal gastrectomy. In a study of 292 patients (PPG 116 patients; distal gastrectomy 176 patients), PPG was associated with better nutritional outcome and lower incidence of gallstones[17]. It is thought that preservation of the hepatic branch of the vagal nerve maintains gallbladder contractility and decreases gallstone formation[23,24]. After gastrectomy, normal gastrointestinal function is compromised and dumping syndrome, which occurs when food is rapidly introduced into the small intestine, occurs after distal gastrectomy on a regular basis. This tends to be lower after PPG[9,25,26]. However, preservation of the infrapyloric artery and the hepatic branch of the vagal nerve, which is essential in PPG for maintaining pyloric function, is technically difficult. In addition, when pyloric function worsens, symptoms related to delayed gastric emptying are a real drawback[27,28].

This KLASS-04 RCT was conducted to show better functional outcome without compromising survival and safety after LPPG in patients with middle-third EGC. The present study showed that patients undergoing LPPG had comparable complication rates after LDG. Whether LPPG is associated with decreased dumping syndrome, bile gastritis and gallstone formation remains to be determined.

Funding

This study was supported by a research fund from Olympus Korea (Bongeunsa-Ro 446, Gangnam-gu, Seoul, Korea).

Disclosure. Do Joong Park - Research Funding: Medtronic, Daewoong Pharmaceutical, Han-Kwang Yang - Research Funding: Stryker,

Sang-Uk Han - Research Funding: Jeil Pharmaceutical, Ethicon Endo-Surgery, Johnson & Johnson, Hyung-Ho Kim - Research Funding: Olympus Korea, Woo Jin Hyung - Employment: Hutom, Leadership: Hutom, Stock and Other Ownership Interests: Hutom, Consulting or Advisory Role: Ethicon, Verb Surgical, Research Funding: Medtronic, GC Pharma, Hyuk-Joon Lee Research Funding: Olympus Korea, JW Pharmaceutical.

Supplementary material

Supplementary material is available at *BJS* online.

References

1. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994;**4**:146–148.
2. Kim HH, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW *et al.*; Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. Effect of laparoscopic distal gastrectomy *vs* open distal gastrectomy on long-term survival among patients with stage I gastric cancer: the KLASS-01 randomized clinical trial. *JAMA Oncol* 2019;**5**:506–513.
3. Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW *et al.* Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). *Ann Surg* 2016;**263**:28–35.
4. Guideline Committee of the Korean Gastric Cancer Association; Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an evidence-based, multi-disciplinary approach. *J Gastric Cancer* 2019;**19**:1–48.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021;**24**:1–21.
6. Maki T, Shiratori T, Hatafuku T, Sugawara K. Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. *Surgery* 1967;**61**:838–845.
7. Oh SY, Lee HJ, Yang HK. Pylorus-preserving gastrectomy for gastric cancer. *J Gastric Cancer* 2016;**16**:63–71.
8. Kong SH, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. The safety of the dissection of lymph node stations 5 and 6 in pylorus-preserving gastrectomy. *Ann Surg Oncol* 2009;**16**:3252–3258.
9. Nunobe S, Sasako M, Saka M, Fukagawa T, Katai H, Sano T. Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer* 2007;**10**:167–172.
10. Park DJ, Lee HJ, Jung HC, Kim WH, Lee KU, Yang HK. Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. *World J Surg* 2008;**32**:1029–1036.
11. Sigstad H. A clinical diagnostic index in the diagnosis of the dumping syndrome. Changes in plasma volume and blood sugar after a test meal. *Acta Med Scand* 2009;**188**:479–486.
12. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al.* The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;**250**:187–196.
13. Oken MM, Creech RH, Tormey DC, Horton J, Davis T E, McFadden ET, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Onco* 1982;**5**:649–655. doi:10.1097/00000421-198212000-00014.
14. Lee HJ, Hyung WJ, Yang HK, Han SU, Park YK, An JY *et al.*; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). *Ann Surg* 2019;**270**:983–991.
15. Edge SB, Byrd DR, Compton CC. AJCC cancer staging handbook, 7th ed. *New York: Springer-Verlag*; 2010.
16. Jiang X, Hiki N, Nunobe S, Fukunaga T, Kumagai K, Nohara K *et al.* Postoperative outcomes and complications after laparoscopy-assisted pylorus-preserving gastrectomy for early gastric cancer. *Ann Surg* 2011;**253**:928–933.
17. Suh YS, Han DS, Kong SH, Kwon S, Shin CI, Kim WH *et al.* Laparoscopy-assisted pylorus-preserving gastrectomy is better than laparoscopy-assisted distal gastrectomy for middle-third early gastric cancer. *Ann Surg* 2014;**259**:485–493.
18. Takahashi R, Ohashi M, Hiki N, Makuuchi R, Ida S, Kumagai K *et al.* Risk factors and prognosis of gastric stasis, a crucial problem after laparoscopic pylorus-preserving gastrectomy for early middle-third gastric cancer. *Gastric Cancer* 2020;**23**:707–715.
19. Tanaka N, Katai H, Saka M, Morita S, Fukagawa T. Laparoscopy-assisted pylorus-preserving gastrectomy: a matched case-control study. *Surg Endosc* 2011;**25**:114–118.
20. Oh SY, Choi B, Lee KG, Choe HN, Lee HJ, Suh YS *et al.* Ultrasonically activated shears reduce blood loss without increasing inflammatory reactions in open distal gastrectomy for cancer: a randomized controlled study. *Ann Surg Oncol* 2017;**24**:494–501.
21. Kodera Y, Yamamura Y, Kanemitsu Y, Shimizu Y, Hirai T, Yasui K *et al.* Lymph node metastasis in cancer of the middle-third stomach: criteria for treatment with a pylorus-preserving gastrectomy. *Surg Today* 2001;**31**:196–203.
22. Kumagai K, Hiki N, Nunobe S, Sekikawa S, Chiba T, Kiyokawa T *et al.* Totally laparoscopic pylorus-preserving gastrectomy for early gastric cancer in the middle stomach: technical report and surgical outcomes. *Gastric Cancer* 2015;**18**:183–187.
23. Kobayashi T, Hisanaga M, Kanehiro H, Yamada Y, Ko S, Nakajima Y. Analysis of risk factors for the development of gallstones after gastrectomy. *Br J Surg* 2005;**92**:1399–1403.
24. Wang CJ, Kong SH, Park JH, Choi JH, Park SH, Zhu CC *et al.* Preservation of hepatic branch of the vagus nerve reduces the risk of gallstone formation after gastrectomy. *Gastric Cancer* 2021;**24**:232–244.
25. Mine S, Sano T, Tsutsumi K, Murakami Y, Ehara K, Saka M *et al.* Large-scale investigation into dumping syndrome after gastrectomy for gastric cancer. *J Am Coll Surg* 2010;**211**:628–636.
26. Nishikawa K, Kawahara H, Yumiba T, Nishida T, Inoue Y, Ito T *et al.* Functional characteristics of the pylorus in patients undergoing pylorus-preserving gastrectomy for early gastric cancer. *Surgery* 2002;**131**:613–624.
27. Kodama M, Koyama K, Chida T, Arakawa A, Tur G. Early postoperative evaluation of pylorus-preserving gastrectomy for gastric cancer. *World J Surg* 1995;**19**:456–461.
28. Sawai K, Takahashi T, Fujioka T, Minato H, Taniguchi H, Yamaguchi T. Pylorus-preserving gastrectomy with radical lymph node dissection based on anatomical variations of the infrapyloric artery. *Am J Surg* 1995;**170**:285–288.