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)

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Objectives: To determine the safety of laparoscopy-assisted distal gastrectomy (LADG) compared with open distal gastrectomy (ODG) in patients with clinical stage I gastric cancer in Korea.

Background: There is still a lack of large-scale, multicenter randomized trials regarding the safety of LADG.

Methods: A large-scale, phase 3, multicenter, prospective randomized controlled trial was conducted. The primary end point was 5-year overall survival. Morbidity within 30 postoperative days and surgical mortality were compared to evaluate the safety of LADG as a secondary end point

Results: A total of 1416 patients were randomly assigned to the LADG group (n = 705) or the ODG group (n = 711) between February 1, 2006, and August 31, 2010, and 1384 patients were analyzed for modified intention-to-treat analysis (ITT) and 1256 were eligible for per protocol (PP) analysis (644 and 612, respectively). In the PP analysis, 6 patients (0.9%) needed open conversion in the LADG group. The overall complication rate was significantly lower in the LADG group (LADG vs ODG; 13.0% vs 19.9%, $P = 0.001$). In detail, the wound complication rate of the LADG group was significantly lower than that of the ODG group (3.1% vs 7.7%, $P < 0.001$). The major intra-abdominal complication (7.6% vs 10.3%, $P = 0.095$) and mortality rates (0.6% vs 0.3%, $P = 0.687$) were similar between the 2 groups. Modified ITT analysis showed similar results with PP analysis.

Conclusions: LADG for patients with clinical stage I gastric cancer is safe and has a benefit of lower occurrence of wound complication compared with conventional ODG.

Keywords: complication, laparoscopy, morbidity, mortality, stomach neoplasm

(*Ann Surg* 2015;xx:xxx–xxx)

Since laparoscopy-assisted distal gastrectomy (LADG) was first reported in 1994, it has been rapidly adopted in Korea and Japan.[1] Many articles have reported the safety and short/long-term oncologic results of this procedure, and the Japanese Laparoscopic Surgery Study Group reported 99.8% and 98.7% disease-free survival in stage IA and IB gastric cancers in their multicenter retrospective study.[2]

Before proving the oncologic safety of new surgical procedures, the operative safety of laparoscopic surgery should be guaranteed. Because laparoscopic surgery has a relatively narrow surgical view and relies on surgical devices such as ultrasonic shears, surgical clips, or endoscopic staplers without tactile sense for surgeons, a safety analysis is essential. Several randomized controlled trials (RCTs) have been conducted to address the controversy and concerns on the safety and oncological outcomes of LADG compared with open distal gastrectomy (ODG) for early gastric cancer (EGC). Those RCTs showed non-inferiority with regard to the postoperative morbidity and the superiority of LADG in terms of reduced pain, earlier recovery, and better quality of life.[3–8] However, controversies persist because most of these studies were single-center studies with small sample size and lacked long-term follow-up results for the evaluation of this new surgical procedure. To provide stronger evidence, the Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group designed this phase 3 multicenter RCT (KLASS-01) to elucidate the oncologic feasibility of LADG versus ODG by comparing 5-year overall survival.[9] We are now reporting the morbidity and mortality data, which are the secondary but important end point in this surgical trial.

METHODS

Study Design and Participants

KLASS-01 was designed as a phase 3, multicenter, open-label, noninferiority, prospective RCT conducted at 13 university hospitals

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Disclosure: Supported by a grant from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (0520310 to Hyung-Ho Kim and 1320270 to Sang-Uk Han). The authors declare no conflicts of interest.

Clinicatrial.gov, NCT00452751

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ISSN: 0003-4932/14/26105-0821

DOI: 10.1097/SLA.0000000000001346

with 15 gastric surgeons in Korea. Interim analysis regarding morbidity and mortality showed no difference between 179 LADG and 163 ODG patients in this trial.[10] The study protocol was approved by the institutional review boards of all of the participating hospitals before initiating the study, and all of the patients provided written informed consent. We included patients 20 to 80 years of age with histologically proven adenocarcinoma of preoperative stage I (cT1N0M0, cT1N1M0, and cT2aN0M0) gastric cancer according to the American Joint Committee on Cancer/Union for International Cancer Control, sixth edition. The preoperative stage was determined by the findings of computed tomography and/or endoscopic ultrasonography. We excluded patients with American Society of Anesthesiologists (ASA) score >3, presence of other malignancies, history of previous chemo- or radiotherapy, and plans to undergo total gastrectomy and/or combined resection except cholecystectomy for gallbladder stone or polyp. The primary endpoint of this study was to elucidate the noninferiority of LADG compared with conventional ODG in terms of 5-year overall survival.

Randomization

After confirming that the patients meet the inclusion/exclusion criteria, informed consent was obtained. The patients were then registered into the trial and randomized to 1 of 2 groups (LADG or ODG) based on a computer-generated randomization list. The randomization was coordinated centrally by the independent data center and aimed to balance the arms according to each institution.

Quality Control

The surgeons participating in the trial were to have conducted at least 50 cases each of LADG and ODG, and each participant's institution was to conduct at least 80 cases each year for surgical quality control. We established a standardized protocol of the procedure, and all of the surgeons' operation quality was assessed by 2 experienced surgeons' site visits. Then, all of the participating surgeons thoroughly reviewed each other participant's unedited videos for the standardization and quality control of the study.

Interventions and Outcome Measurement

A standard radical distal gastrectomy with D1 + β (nos. 1, 3, 4d, 4sb, 5, 6, 7, 8a, and 9) or D2 according to the Japanese classification was done in both groups.[11] Dissection of lymph node station 14 v was optional, and a partial omentectomy was carried out. Reconstruction was selected from among standard Billroth I/II (B-I/II) or Roux-en-Y fashion, depending on the surgeon's preference. During the laparoscopic surgery, the number and position of trocar placements were not limited. In both arms, placement of drain and drain removal were decided by the operator. Drain amylase was checked on postoperative days (PODs) 1, 2, and 5.

During the perioperative periods, all of the patients were managed by a standardized clinical pathway, and discharge was recommended when the patients tolerated more than 2 days of soft diet without abdominal pain or fever. Retrieved data included the ASA score, comorbidities, laboratory findings, progression of oral intake, degree of pain evaluated by the visual analog scale, and transfusions received. All of the surgical and medical complications and mortality events were documented. Surgical complications were confined to events that occurred within 30 days after the surgery; these included wound complications, fluid collection/abscesses, intra-abdominal bleeding, intraluminal bleeding, ileus, intestinal obstruction, anastomotic stenosis and leakage, enterocutaneous or pancreatic fistulas, and pancreatitis. Medical complications included pulmonary, urinary, renal, hepatic, cardiac, and endocrine events. We defined pancreatic fistula as a drain amylase level greater than 1000 IU/L after POD#3.[9] Intestinal obstruction and ileus are defined as no return of bowel movement until POD#5. To be specific, intestinal obstruction is defined as definite mechanical obstruction confirmed by air–fluid level of plain x-ray or obstruction point by computed tomography. Only paralytic ileus and bowel dilatation without definite mechanical obstruction point were considered as a true ileus. During surgery, the operative time and the intraoperative blood loss (calculated by the volume of suction and the weight of gauze) were recorded. To ensure accurate quantification of operative blood loss, irrigation during surgery was not recommended if possible. Mortality was defined as any death that occurred during the hospital stay and/or any death related to any surgery-related complications.

Statistical Analysis

Baseline statistical background of this trial and sample-size calculation were described previously in the trial note.[9] A noninferiority hypothesis would not be adopted in comparison of morbidity and mortality between 2 surgical modalities in this article.

We defined 2 different populations for analysis. One population is the modified intention-to-treat (ITT) group, which excluded patients who had been randomized and met postrandomization exclusion criteria. The other population is a per protocol (PP) population for morbidity and mortality. The patients who switched to the other group's approach (eg, intentionally received laparoscopic surgery after being allocated to the open group), underwent any other surgery besides distal gastrectomy, or combined resection except cholecystectomy were not included in the PP population for morbidity and mortality analyses. Both populations were used for the statistical analysis of patient demographics and surgical results. With regard to the mortality, reoperation, and risk factor analysis, the PP analysis was mainly used to examine the comparisons of pure results after LADG and ODG.

The incidence of operative morbidity and mortality were expressed as the number of cases divided by the total number of registered patients. The comparisons among groups were evaluated with Student *t* test, the χ^2 test, and Fisher exact test. The multivariate analysis to determine independent risk factors for postoperative complications was conducted with a binary logistic regression analysis. *P* values less than 0.05 were considered significant. All of the statistical analyses were conducted with SPSS (version 18.0). This trial is registered with ClinicalTrials.gov (number NCT00452751).

RESULTS

Figure 1 shows the trial flow chart. Between February 1, 2006, and August 31, 2010, 1416 patients were enrolled and randomly allocated to groups. For the modified ITT analysis, 32 patients were excluded. These patients met postrandomization exclusion criteria: 18 withdrew consent, 5 underwent proximal gastrectomies, 5 underwent robotic gastrectomies, 6 had synchronous malignancies, and 1 had a history of a gastric cancer operation. In addition, 85 patients who switched to the other group's approach, 23 total gastrectomies, 19 combined resections other than cholecystectomy, and 1 nonresection case due to peritoneal carcinomatosis were excluded for the PP analysis.

Patient demographics and baseline characteristics, including sex, age, body mass index, ASA score, comorbidities, tumor location, size, and clinical and pathologic stages, were well balanced between the 2 groups (Table 1). In terms of the surgical outcomes in the PP population, more Billroth-I reconstructions and D2 lymph node dissections were carried out in the ODG group than in the LADG group. LADG was associated with significantly longer operation time (LADG vs ODG: 184.1 ± 53.3 vs 139.4 ± 42.7, $P < 0.001$), less estimated blood loss (110.8 ± 135.7 vs 190.6 ± 156.3, $P < 0.001$), a shorter hospital stay (7.1 ± 3.1 vs 7.9 ± 4.1, $P < 0.001$), and a smaller number of retrieved lymph nodes (40.5 ± 15.3 vs 43.7 ± 15.7, $P < 0.001$) (Table 2). There were 4 patients in the LADG group

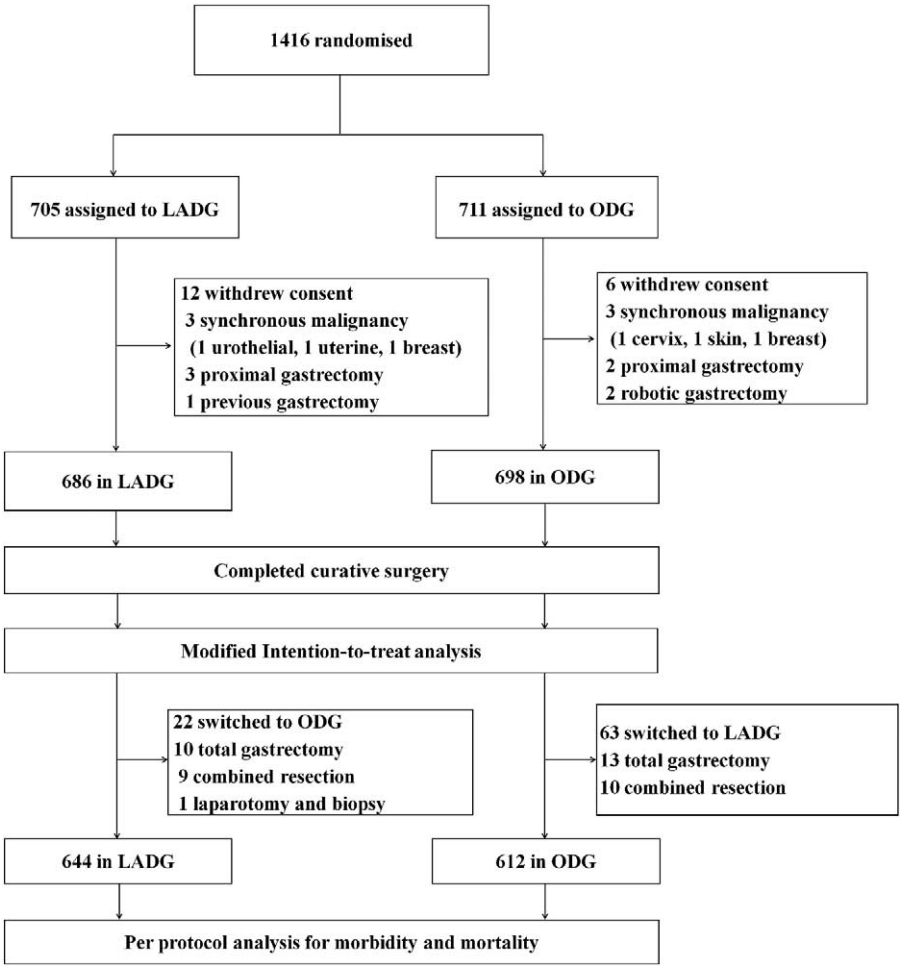

FIGURE 1. Study flow chart. LADG indicates laparoscopy-assisted distal gastrectomy; ODG, open distal gastrectomy.

and 3 patients in the ODG group who had less than 15 lymph nodes retrieved. During surgery, 6 (0.9%) patients who were undergoing LADG were converted to open surgery because of dense adhesions that obscured the operative procedure (n = 3), bleeding from an injured splenic artery (n = 2), or common bile duct injury (n = 1).

In the PP analysis, the overall complication rate within 30 postoperative days was significantly lower in the LADG group compared with the ODG group (13.0% vs 19.9%, $P = 0.001$) (Table 3). In the comparisons for each subtype of complication, no difference was observed in the intra-abdominal surgical complications, including fluid collection/abscess, intra-abdominal bleeding, intraluminal bleeding, anastomotic leakage, intestinal obstruction, and medical complications. However, the incidence of wound complications was significantly lower in the LADG group than in the ODG group (3.1% vs 7.7%, $P < 0.001$); wound dehiscence showed the most pronounced difference. One patient with wound evisceration underwent reoperative fascia closure with general anesthesia. Sixteen patients (LADG 3, ODG 13) with wound dehiscence were managed with frequent dressings, and 14 of them received wound repair under local anesthesia.

With regard to postoperative mortality, there were 4 deaths (0.6%) and 2 deaths (0.3%) in the LADG and ODG groups, respectively. Common leading causes were anastomotic leakage and pneumonia (Table 4). Although the hospital mortality rate appeared to be higher in the LADG group, there was no statistical significance ($P = 0.687$).

Reoperations were required in 8 (1.2%) and 9 (1.5%) patients in the LADG and ODG groups, respectively ($P = 0.726$). One case of wound evisceration in the ODG group required reoperation under general anesthesia. Intra-abdominal bleeding was the most common cause of reoperation in both groups (LADG vs ODG: 4 [0.6%] vs 4 [0.7%]), and the peri-pancreatic head area was the most vulnerable site. One case of omental bleeding occurred in each group. Intraluminal bleeding from the staple line was controlled by suturing. Two afferent loop obstructions in the LADG group and 1 small bowel adhesion in the ODG group were the causes of reoperation for intestinal obstruction. Reoperations for anastomotic leakage were only carried out in the ODG group; the leakages were at the gastroduodenostomy site in 2 patients (Table 5).

In the risk factor analysis, the pathologic stage, type of reconstruction, and extent of lymph node dissection had no significant influences on development of postoperative morbidity. In addition, the operative approach (OR: LADG 0.599, 95% confidence interval [CI]: 0.441–0.813; $P = 0.001$) and number of comorbidities (OR: ≥3 3.602, 95% CI: 1.508–8.662; $P = 0.004$) were revealed as independent risk factors for postoperative morbidity on multivariate analysis (Table 6).

DISCUSSION

An interim analysis of the KLASS-01 trial described that the immediate postoperative morbidity was not significantly different between LADG (11.6%) and ODG (15.1%).[10] In addition, several

Table 1. Patient Demographics and Baseline Characteristics

Variables	Modified Intention-to-treat Population			Per Protocol Population		
	LADG (n = 686)	ODG (n = 698)	*P*	LADG (n = 644)	ODG (n = 612)	*P*
Sex						
Male	453 (66.0%)	465 (66.6%)	0.818	425 (66.0%)	412 (67.3%)	0.618
Female	233 (34.0%)	233 (33.4%)		219 (34.0%)	200 (32.7%)	
Age, yr	56.8 ± 10.9	57.6 ± 11.3	0.172	56.8 ± 10.9	57.8 ± 11.2	0.105
BMI, kg/m^2	23.8 ± 3.0	23.8 ± 3.0	0.992	23.8 ± 2.9	23.8 ± 3.0	0.920
ASA score						
1	343 (50.0%)	347 (49.7%)	0.771	319 (59.5%)	302 (49.3%)	0.830
2	306 (44.6%)	320 (45.8%)		291 (45.2%)	282 (46.1%)	
3	37 (5.4%)	31 (4.4%)		34 (5.3%)	28 (4.6%)	
No. comorbidities						
0	376 (54.8%)	382 (54.7%)	0.862	352 (54.7%)	344 (56.2%)	0.946
1	218 (31.8%)	227 (32.5%)		209 (32.5%)	194 (31.7%)	
2	77 (11.2%)	78 (11.2%)		70 (10.9%)	63 (10.3%)	
≥3	15 (2.1%)	11 (1.6%)		13 (2.0%)	11 (1.8%)	
Comorbidity						
Hypertension	191 (27.8%)	201 (28.8%)		180 (28.0%)	165 (27.0%)	
Diabetes	80 (11.7%)	87 (12.5%)		75 (11.6%)	73 (11.9%)	
Pulmonary	15 (2.2%)	16 (2.3%)		15 (2.3%)	13 (2.1%)	
CVD	25 (3.6%)	23 (3.3%)		22 (3.4%)	20 (3.3%)	
Renal	5 (0.7%)	5 (0.7%)		5 (0.8%)	5 (0.8%)	
Hepatic	31 (4.5%)	27 (3.9%)		28 (4.3%)	23 (3.8%)	
Cerebrovascular	10 (1.4%)	13 (1.9%)		10 (1.6%)	13 (2.1%)	
Tuberculosis	14 (2.0%)	11 (1.6%)		11 (1.7%)	11 (1.8%)	
Others	48 (7.0%)	34 (4.9%)		44 (6.8%)	31 (5.1%)	
Tumor location*						
Upper	7 (1.0%)	14 (2.1%)	0.484	4 (0.6%)	5 (0.8%)	0.927
Middle	207 (31.0%)	204 (29.9)		195 (31.1%)	184 (30.8%)	
Lower	452 (67.7%)	463 (67.9%)		428 (68.3%)	408 (68.3%)	
Whole	2 (0.3%)	1 (0.1%)				
Tumor size (mm)	27.2 ± 18.5	27.6 ± 17.1	0.629	25.9 ± 15.1	27.1 ± 16.4	0.195
cTNM stage						
cT1N0M0	537 (78.3%)	541 (77.5%)	0.925	510 (79.2%)	467 (76.3%)	0.417
cT1N1M0	17 (2.5%)	19 (2.7%)		15 (2.3%)	19 (3.1%)	
cT2aN0M0	132 (19.2%)	138 (19.8%)		119 (18.5%)	126 (20.6%)	
pT-stage†						
Tis	2 (0.3%)	3 (0.4%)	0.885	2 (0.3%)	3 (0.5%)	0.431
T1	553 (80.7%)	549 (78.8%)		524 (81.4%)	479 (78.4%)	
Mucosa	318 (46.4%)	308 (44.2%)		304 (47.2%)	272 (44.5%)	
Submucosa	235 (34.3%)	241 (34.6%)		220 (34.2%)	207 (33.9%)	
T2a	75 (10.9%)	75 (10.8%)		74 (11.5%)	67 (11.0%)	
T2b	33 (4.8%)	41 (5.9%)		27 (4.2%)	37 (6.1%)	
T3	17 (2.5%)	24 (3.4%)		12 (1.9%)	21 (3.4%)	
T4	0 (0%)	1 (0.1%)		0 (0%)	0 (0%)	
Tx‡	5 (0.7%)	5 (0.7%)		5 (0.8%)	5 (0.8%)	
pN-stage†						
N0	582 (85.0%)	582 (83.4%)	0.833	552 (85.7%)	510 (83.3%)	0.391
N1 (1–6)	86 (12.6%)	95 (13.6%)		78 (12.1%)	84 (13.7%)	
N2 (7–15)	13 (1.9%)	15 (2.1%)		12 (1.9%)	12 (2.0%)	
N3 (16-)	4 (0.6%)	6 (0.9%)		2 (0.3%)	6 (1.0%)	
pStage						
IA	511 (74.5%)	511 (73.2%)	0.769	487 (75.6%)	445 (72.7%)	0.445
IB	112 (16.3%)	106 (15.2%)		104 (16.1%)	98 (16.0%)	
II	40 (5.8%)	52 (7.4%)		35 (5.4%)	43 (7.0%)	
IIIA	15 (2.2%)	17 (2.4%)		14 (2.2%)	16 (2.6%)	
IIIB	3 (0.4%)	5 (0.7%)		2 (0.3%)	4 (0.7%)	
IV	5 (0.7%)	7 (1.0%)		2 (0.3%)	6 (1.0%)	

Data are n/N (%) or mean ± standard deviation.

*Missing data at tumor location: mITT – LADG (18), ODG (16); PP – LADG (17), ODG (15).

†T and N stage are based on the UICC 6th edition. One case of T and N stage is missing from the modified intention-to-treat population (LADG group) because this case did not receive curative resection due to peritoneal carcinomatosis (see Fig. 1).

‡No residual tumor in permanent pathology.

BMI indicates body mass index; CVD, cardiovascular disease except hypertension.

Table 2. Surgical Results

Variables	Modified Intention-to-treat Population			Per Protocol Population		
	LADG (n = 686)	ODG (n = 698)	*P*	LADG (n = 644)	ODG (n = 612)	*P*
Extent of resection						
Distal gastrectomy	675 (98.4%)	685 (98.1%)	0.605	644 (100%)	612 (100%)	1.00
Total gastrectomy	10 (1.5%)	13 (1.9%)				
Laparotomy and biopsy	1 (0.1%)	0 (0%)				
Reconstruction*						
Billroth-I	433 (63.2%)	502 (71.9%)	<0.001	413 (64.1%)	454 (74.2%)	<0.001
Billroth-II	232 (33.9%)	163 (23.4%)		222 (34.5%)	142 (23.2%)	
Roux-en-Y	20 (2.9%)	33 (4.7%)		9 (1.4%)	16 (2.6%)	
Lymph node dissection*						
D1 + α	1 (0.1%)	1 (0.1%)	0.003	1 (0.2%)	1 (0.2%)	0.002
D1 + β	300 (43.7%)	249 (35.7%)		283 (44.1%)	215 (35.1%)	
D2	384 (56.0%)	448 (64.2%)		360 (55.7%)	396 (64.7%)	
Combined resection	37 (5.4%)	37 (5.3%)	0.939			
Gall bladder	24 (3.5%)	25 (3.6%)	0.472	20 (3.1%)	24 (3.9%)	0.432
Spleen	5 (0.7%)	1 (0.1%)				
Colon	0 (0%)	1 (0.1%)				
Adrenal	1 (0.1%)	1 (0.1%)				
Ovary	2 (0.3%)	1 (0.1%)				
Others†	5 (0.6%)	8 (1.1%)				
Operation time (min)	184.7 ± 55.0	145.8 ± 49.4	<0.001	184.1 ± 53.3	139.4 ± 42.7	<0.001
Estimated blood loss (mL)	118.6 ± 149.0	194.2 ± 166.3	<0.001	190.6 ± 156.3	<0.001	
Intraoperative transfusion						
No	681 (99.3%)	690 (98.9%)	0.421	640 (99.4%)	606 (99.0%)	0.474
Yes	5 (0.7%)	8 (1.1%)		4 (0.6%)	6 (1.0%)	
No. retrieved lymph nodes	40.5 ± 15.2	43.3 ± 15.7	0.001	40.5 ± 15.3	43.7 ± 15.7	<0.001
Hospital stay (d)	7.2 ± 3.2	8.0 ± 4.3	<0.001	7.1 ± 3.1	7.9 ± 4.1	<0.001

Data are n/N (%) or mean ± standard deviation.

*One missing data at reconstruction and lymph node dissection in mITT LADG group (peritoneal carcinomatosis).

†Others (ODG: 3 appendectomy-appendicolith, 1 ileocecectomy-appendiceal mucocele, 1 hysterectomy-myoma, 1 duodenal bulb diverticulectomy, 1 ampullectomy-tubular adenoma, 1 cholecystectomy with appendectomy-GB stone and appendicolith, LADG: 1 hysterectomy-myoma, 1 pancreas body wedge resection-adhesion, 1 small bowel resection–adhesion and stricture).

Table 3. Postoperative Morbidity Within 30 Postoperative Days

Variables	Modified Intention-to-treat Population			Per Protocol Population		
	LADG (n = 686)	ODG (n = 698)	*P*	LADG (n = 644)	ODG (n = 612)	*P*
No. postoperative morbidity	94 (13.7%)	132 (18.9%)	0.009	84 (13.0%)	122 (19.9%)	0.001
Intra-abdominal complication	54 (7.9%)	70 (10.0%)	0.160	49 (7.6%)	63 (10.3%)	0.095
Fluid collection/abscess	6 (0.9%)	8 (1.1%)	0.614	4 (0.6%)	8 (1.3%)	0.212
Intra-abdominal bleeding	14 (2.0%)	16 (2.3%)	0.748	12 (1.9%)	14 (2.3%)	0.598
Intraluminal bleeding	4 (0.6%)	11 (1.6%)	0.074	4 (0.6%)	8 (1.3%)	0.212
Anastomotic leakage	5 (0.7%)	7 (1.0%)	0.583	5 (0.8%)	4 (0.7%)	1.000
Intestinal obstruction	3 (0.4%)	2 (0.3%)	0.684	3 (0.5%)	2 (0.3%)	1.000
Ileus	13 (1.9%)	18 (2.6%)	0.390	12 (1.9%)	18 (2.9%)	0.211
Stenosis	2 (0.3%)	1 (0.1%)	0.621	2 (0.3%)	1 (0.2%)	1.000
Stasis	7 (1.0%)	10 (1.4%)	0.486	7 (1.1%)	10 (1.6%)	0.402
Pancreatitis	1 (0.1%)	0 (0%)	0.496	1 (0.2%)	0 (0%)	1.000
Cholecystits	0 (0%)	1 (0.1%)	1.000	0 (0%)	1 (0.2%)	0.487
Idiopathic small bowel perforation	1 (0.1%)	0 (0%)	0.496	1 (0.1%)	0 (0%)	0.313
Wound complication	25 (3.6%)	49 (7.0%)	0.005	20 (3.1%)	47 (7.7%)	<0.001
Seroma	12 (1.7%)	22 (3.2%)	0.092	10 (1.6%)	21 (3.4%)	0.032
Hematoma	3 (0.4%)	6 (0.9%)	0.507	2 (0.3%)	6 (1.0%)	0.168
Infection	7 (1.0%)	7 (1.0%)	0.974	5 (0.8%)	6 (1.0%)	0.698
Dehiscence	3 (0.4%)	13 (1.9%)	0.013	3 (0.5%)	13 (2.1%)	0.009
Evisceration	0 (0%)	1 (0.1%)	1.000	0 (0%)	1 (0.1%)	0.487
Medical complications	19 (2.8%)	20 (2.9%)	0.914	19 (3.0%)	18 (2.9%)	0.992
Respiratory	5 (0.7%)	11 (1.6%)		5 (0.8%)	10 (1.6%)	
Cardiovascular	3 (0.4%)	2 (0.3%)		3 (0.5%)	2 (0.3%)	
Hepatic	0 (0%)	2 (0.3%)		0 (0%)	2 (0.3%)	
Renal	3 (0.4%)	0 (0%)		3 (0.5%)	0 (0%)	
Urinary	4 (0.6%)	2 (0.3%)		4 (0.6%)	1 (0.2%)	
Metabolic	0 (0%)	1 (0.1%)		0 (0%)	1 (0.2%)	
Gastrointestinal	3 (0.4%)	2 (0.3%)		3 (0.5%)	2 (0.3%)	
Viral infection	2 (0.3%)	0 (0%)		2 (0.3%)	0 (0%)	

Table 4. Mortality Cases

Group*	Sex	Age	Comorbidities	Reconstruction	Primary Cause of Death	Date of Death (POD)
LADG (0.6%)	Male	71	Pulmonary, hypertension	B-I	Anastomotic leakage, aspiration pneumonia	49
	Male	51	Hepatic	B-II	Pneumonia, idiopathic small bowel perforation	30
	Male	64	Renal, hepatic, diabetic	B-II	ARF, duodenal stump leakage	31
	Female	66	None	B-I	Adhesive ileus, sudden respiratory failure	37
ODG (0.3%)	Male	71	None	B-II	Pneumonia, ARDS	61
	Male	73	Hypertension, diabetic	B-I	Anastomotic leakage, sepsis	31

*$P = 0.687$.
ARDS indicates acute respiratory distress syndrome; ARF, acute renal failure.

previous clinical reports have shown the noninferiority of laparoscopic surgery compared with conventional open gastrectomy (OG) in terms of postoperative morbidity. According to single-center studies, the morbidity rates ranged from 4.2% to 23.3% after laparoscopic gastrectomy (LG), and there was no difference compared with OG.[8,10,12–16] A retrospective multicenter study for LG by the Japanese Laparoscopic Surgery Study and KLASS groups reported morbidity rates of 14.8% and 15.1%, respectively.[2,17] A recent meta-analysis for all of the RCTs comparing LADG versus ODG revealed favorable results for LADG (OR: 0.5; 95% CI 0.31–0.80; $P = 0.004$) in terms of postoperative complications.[18]

The present RCT, recruiting the largest scale of patients to date, showed significantly lower morbidity rate in the LADG patients. When the morbidity rate was analyzed according to each complication type, the proportion of wound-related complications was significantly higher in the ODG group compared with intra-abdominal or medical complications. These results could suggest that longer length with prolonged traction of the abdominal wound during conventional OG would lead to a significantly higher wound-related morbidity rate compared with LG. In addition, hospital stay was longer in patients with wound complications than those without wound complications. (8.7 ± 3.5 vs 7.4 ± 3.6, $P = 0.007$)

One predicted defective point was postoperative bleeding due to an inability to apply surgical ties to the dissected plane or vessels during LADG. Instead, an ultrasonic device, hemoclips, or endoscopic staplers was usually used, and these devices are guaranteed by their own RCTs. Other RCTs regarding colorectal cancer surgery comparing conventional open and laparoscopic colorectal surgery also showed no differences in postoperative bleeding.[19,20] In the present study, 4 patients in each group underwent reoperations for bleeding; there was no significant difference in the patients requiring reoperations.

The incidence of pancreatic fistula after LADG is known to be 1% to 4.3%.[21,22] However, there was no pancreatic fistula in our study. This may be due to the difference in the definition of pancreatic fistula. According to the definition of the International Study Group of Pancreatic Fistula, a recent pancreatic fistula is diagnosed when the drain amylase level is over 3 times the serum amylase level on POD#3.[23] When our trial was designed, there were no consensus guidelines for pancreatic fistula. There may be a discrepancy in the result of pancreatic fistula with the recent definition. Moreover, the incidence of pancreatic fistula might have been underestimated because the duration of abdominal drain maintenance and the monitoring of drain amylase were determined by the surgeon under individual clinical circumferences. Nevertheless, because most patients showed a transient elevation of drain amylase (grade A) without symptoms, we followed our definition.

Table 5. Reoperation Cases

Variables	LADG (n = 644)	ODG (n = 612)	*P*
Reoperation	8 (1.2%)	9 (1.5%)	0.726
Wound evisceration	0 (0)	1 (0.2%)	
Intra-abdominal bleeding	4 (0.6%)	4 (0.7%)	
Peri-pancreatic head area	2	3	
Perigastric vessel	1	0	
Omental bleeding	1	1	
Intraluminal bleeding	1 (0.2%)	1 (0.2%)	
Intestinal obstruction	2 (0.3%)	1 (0.2%)	
Anastomotic leakage	0 (0%)	2 (0.3%)	
Idiopathic delayed small bowel perforation	1 (0.2%)	0 (0%)	

The postoperative mortality rate ranges from 0% to 3.5% after LG for gastric cancer in single-center studies, and multicenter retrospective studies in Korea and Japan showed rates of 0.5% and 0%, respectively.[2,10,12–17] In the present study, there were operation-related deaths in 4 (0.6%) and 2 (0.3%) patients in the LADG and ODG groups ($P = 0.687$), respectively. Postoperative deaths were caused by aspiration pneumonia, idiopathic small bowel perforation and sepsis, hepatic failure, and sudden respiratory failure in the LADG group, and by postoperative pneumonia and anastomotic leakage followed by aspiration pneumonia in the ODG group. The most common causes were pneumonia and anastomotic leakage. Some previous studies insisted that LADG had an advantage of fewer pulmonary complications.[6,8] However, there was no difference in the development of pulmonary complications and related mortalities. There was 1 case of idiopathic small bowel perforation in the LADG group. Although its cause was not fully identified, 1 possible explanation focuses on the device used in the LADG group. Ultrasonic activated scissors have gained widespread enthusiasm among laparoscopic surgeons. However, thermal injury from this tool is often neglected, which can cause delayed presentations of injury.[24] It is important that, during the use of the ultrasonic shear, the active blade of the device should always be within laparoscopic view.

The surgical outcomes of the present clinical trial showed that blood loss during the operation in the LADG group was significantly less than in the ODG group. Other reports, including a retrospective KLASS study, showed similar results.[13,14,17,18,25,26] One of the definite benefits of laparoscopic surgery is the ability to observe the surgical field in a magnified view through the monitor. This visualization could lead to more meticulous dissection to prevent unexpected bleeding in laparoscopic surgery compared with open procedures. On the other hand, because laparoscopic procedures are more complicated, even a small amount of bleeding could easily interrupt the surgical field, thus, leading to more frequent bleeding control. In the present study, the operation time in the LADG group was approximately 40 minutes longer than in the ODG group. Although skilled surgeons participated in this trial, the meticulous dissection and frequent bleeding control were responsible for the longer procedure time in the LADG group. In addition, time for changing instruments, a narrow surgical field with a limited assistant's role, and repeated procedures, such as carrying out a minilaparotomy and repneumoperitoneum during the anastomosis or specimen retrieval, could have increased the overall operative time.

Table 6. Univariate and Multivariate Analyses of Risk Factors for Postoperative Morbidity

		Univariate Analysis		Multivariate Analysis	
Variables	**No. (n = 1256)**	**Morbidity (n = 206)**	***P***	**Odds Ratio**	***P***
Operative approach					
Open	612	122 (19.9%)	0.001	1	0.001
Laparoscopy	644	84 (13.0%)		0.599 (0.441–0.813)	
Age, yr					
<60	690	100 (14.5%)	0.044	1	0.348
≥60	566	106 (18.7%)		1.164 (0.848–1.616)	
Sex					
Male	837	146 (17.4%)	0.159		
Female	419	60 (14.3%)			
BMI, kg/m^2					
<25	823	132 (16.0%)	0.135		
25–30	407	66 (16.2%)			
≥30	26	8 (30.8%)			
No. comorbidities					0.013
0	696	97 (13.9%)	0.003	1	
1	403	72 (17.9%)		1.307 (0.927–1.843)	0.126
2	133	28 (21.1%)		1.578 (0.970–2.588)	0.066
≥3	24	9 (37.5%)		3.602 (1.508–8.662)	0.004
Reconstruction type					
Billroth-I	867	133 (15.3%)	0.312		
Billroth-II	364	68 (18.7%)			
Roux-en-Y	25	5 (20.0%)			
Lymph node dissection					
≤D1 + β	500	74 (14.8%)	0.213		
D2	756	132 (17.5%)			
Intraoperative transfusion					
Yes	10	2 (20.0%)	0.758		
No	1246	204 (16.4%)			
Operation time (min)					
<150	559	81 (14.5%)	0.101		
1504	697	125 (17.9%)			
pT stage					
T1	1018	159 (15.6%)	0.121		
≥T2	238	47 (19.7%)			
pN stage					
N0	1062	175 (16.5%)	0.863		
N1–3	194	31 (16.0%)			
pStage					
I	932	149 (16.0%)	0.501		
II–IV	324	57 (17.6%)			

Retrospective multicenter data from the KLASS group reported that the patients' comorbidities and a lack of surgeon's experience were independent risk factors for predicting postoperative complications.[27] In contrast to this previous report that collected the surgical results from initial cases of participating surgeons, only experienced surgeons participated in this clinical trial. To maintain the surgical quality in the present study, 2 expert surgeons visited each institution and assessed the surgeon's eligibility for participation. Therefore, we did not consider surgeon's experience to be a risk factor for predicting postoperative morbidity in the statistical analysis for this study. In addition, the number of comorbidities was the most important independent factor for predicting postoperative morbidity in both procedures.

In our study, approximately 10% of patients who were initially thought to have stage I cancer turned out to have stage II or higher cancer on final pathology reports. Inclusion of these advanced patients may not affect morbidity and mortality values, but the 5-year survival rate might be less than the initial estimations.

In the modified ITT group, surgical method was switched in 22 patients from LADG to ODG, whereas in 63 patients, it was switched from ODG to LADG. This trend may have been influenced by the patients' preference for laparoscopic surgery at the time of trial initiation, because laparoscopic surgeries were gradually gaining popularity when the KLASS-01 study started. This protocol violation is one of the major limitations of our study. We have presented both the modified ITT and PP results to compensate for this.

Because there were no limitations in the extent of lymph node dissection and reconstruction methods, significant differences were shown between the 2 groups. As the participating surgeons in this study were familiar with laparoscopic gastric cancer surgery, they were already skilled with D2 lymph node dissection—the basic procedure in open gastrectomy. This might make a difference in the proportion of D2 lymph node dissection. However, D1 + β lymph node dissection was also a suitable operation in our study population. These differences might have biased our results. However, there were no differences in the incidence of complications with regard to the lymph node dissection and reconstruction method.

CONCLUSIONS

The incidence of postoperative morbidity in the LADG group was significantly lower than that in the ODG group. This finding suggests that

LADG is surgically safe for the treatment of stage I gastric cancer and has benefits with regard to minimizing wound complications.

ACKNOWLEDGMENTS

The authors thank the members of the data safety and monitoring board, especially Sang-Yong Son, MD, and A Young Kim, for data collection and validation. The authors also thank Dong Jin Kim, MD, and Hoon Hur, MD, for assistance with data management and analysis. The authors are grateful to all of the patients who volunteered to participate in this trial.

Author contributions: W. Kim, H.-J. Lee: conception and design; all authors: collection and assembly of data; S.-U. Han, M.-C. Kim, W. J. Hyung, S. W. Ryu, G. S. Cho, C. Y. Kim, H.-K. Yang, D. J. Park, K. Y. Song, S. I. Lee, S. Y. Ryu, J.-H. Lee: data analysis and interpretation; Kim, Woo Jin Hyung, Seung Wan Ryu, Gyu Seok Cho, Chan Young Kim, Han-Kwang Yang, Do Joong Park, Kyo Young Song, Sang Il Lee, Seung Yub Ryu, and Joo-Ho Lee; all authors: manuscript writing; all authors: final approval of manuscript; H.-H. Kim, H.-K. Yang: administrative support.

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