original reports

Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial

Woo Jin Hyung, MD, PhD[1]; Han-Kwang Yang, MD, PhD[2]; Young-Kyu Park, MD, PhD[3]; Hyuk-Joon Lee, MD, PhD[2]; Ji Yeong An, MD, PhD[1]; Wook Kim, MD[4]; Hyoung-Il Kim, MD[1]; Hyung-Ho Kim, MD[5]; Seung Wan Ryu, MD[6]; Hoon Hur, MD[7]; Min-Chan Kim, MD[8]; Seong-Ho Kong, MD[2]; Gyu Seok Cho, MD[9]; Jin-Jo Kim, MD, PhD[10]; Do Joong Park, MD, PhD[5]; Keun Won Ryu, MD, PhD[11]; Young Woo Kim, MD, PhD[11]; Jong Won Kim, MD[12]; Joo-Ho Lee, MD, PhD[13]; and Sang-Uk Han, MD, PhD[7] on behalf of the Korean Laparoendoscopic Gastrointestinal Surgery Study Group

abstract

PURPOSE It is unclear whether laparoscopic distal gastrectomy for locally advanced gastric cancer is oncologically equivalent to open distal gastrectomy. The noninferiority of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer compared with open surgery in terms of 3-year relapse-free survival rate was evaluated.

PATIENTS AND METHODS A phase III, open-label, randomized controlled trial was conducted for patients with histologically proven locally advanced gastric adenocarcinoma suitable for distal subtotal gastrectomy. The primary end point was the 3-year relapse-free survival rate; the upper limit of the hazard ratio (HR) for noninferiority was 1.43 between the laparoscopic and open distal gastrectomy groups.

RESULTS From November 2011 to April 2015, 1,050 patients were randomly assigned to laparoscopy (n = 524) or open surgery (n = 526). After exclusions, 492 patients underwent laparoscopic surgery and 482 underwent open surgery and were included in the analysis. The laparoscopy group, compared with the open surgery group, suffered fewer early complications (15.7% *v* 23.4%, respectively; $P = .0027$) and late complications (4.7% *v* 9.5%, respectively; $P = .0038$), particularly intestinal obstruction (2.0% *v* 4.4%, respectively; $P = .0447$). The 3-year relapse-free survival rate was 80.3% (95% CI, 76.0% to 85.0%) for the laparoscopy group and 81.3% (95% CI, 77.0% to 85.0%; log-rank $P = .726$) for the open group. Cox regression analysis after stratification by the surgeon revealed an HR of 1.035 (95% CI, 0.762 to 1.406; log-rank $P = .827$; P for noninferiority = .039). When stratified by pathologic stage, the HR was 1.020 (95% CI, 0.751 to 1.385; log-rank $P = .900$; P for noninferiority = .030).

CONCLUSION Laparoscopic distal gastrectomy with D2 lymphadenectomy was comparable to open surgery in terms of relapse-free survival for patients with locally advanced gastric cancer. Laparoscopic distal gastrectomy with D2 lymphadenectomy could be a potential standard treatment option for locally advanced gastric cancer.

J Clin Oncol 38:3304-3313. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 15, 2020 and published at ascopubs.org/journal/jco on August 20, 2020: DOI https://doi.org/10.1200/JCO.20.01210

INTRODUCTION

Laparoscopic gastrectomy is an accepted treatment option for gastric cancer with its better short-term outcomes and similar long-term oncologic outcomes, especially for early-stage gastric cancer.[1-4] Previously, the Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) group conducted a randomized trial (KLASS-01) that compared laparoscopic distal gastrectomy with open distal gastrectomy for clinical stage I gastric cancer.[5,6] It demonstrated both the short-term benefits of less blood loss and postoperative pain, faster recovery, and shorter hospital stay and the oncologic safety of laparoscopy, similar to the results of most randomized trials.[7,8]

The oncologic safety of laparoscopic gastrectomy for locally advanced gastric cancer, however, remains controversial. Concerns include high wound and trocar site recurrence rates as a result of carbon dioxide (CO_2) pneumoperitoneum[9] and technical difficulties regarding adequate cancerous organs or tissue manipulation during D2 lymphadenectomy. To our knowledge, this KLASS-02-RCT study was the first large-scale multicenter prospective randomized trial designed to provide evidence of the surgical and oncologic safety of laparoscopic gastrectomy for locally advanced gastric

CONTEXT

Key Objective

Is the long-term survival achieved with laparoscopic distal gastrectomy noninferior to that with open distal gastrectomy in patients with locally advanced gastric cancer?

Knowledge Generated

The 3-year relapse-free survival rates were 80.3% for the laparoscopy group and 81.3% for the open surgery group (log-rank $P = .73$). Cox regression analysis after stratification by the surgeon revealed a hazard ratio of 1.035 (95% CI, 0.762 to 1.406; log-rank $P = .827$; P for noninferiority = .039), which confirmed the noninferiority of the laparoscopic approach in comparison with the open approach.

Relevance

Laparoscopic distal gastrectomy is oncologically safe and can be recommended as a potential standard treatment of locally advanced gastric cancer.

cancer, and similar studies were started just after enrollment of patients for the current study commenced.[10,11]

We hypothesized that laparoscopic distal gastrectomy for locally advanced gastric cancer is noninferior to open surgery with respect to the 3-year relapse-free survival rate.[12] Previously, we reported the short-term benefits of laparoscopic distal gastrectomy for locally advanced gastric cancer compared with open surgery and demonstrated that it is a surgically safe procedure.[13] Here, we present the oncologic outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer by comparing relapse-free survival, recurrence rate, and overall survival with those of open distal gastrectomy.

PATIENTS AND METHODS

Study Design

KLASS-02-RCT was an investigator-initiated, phase III, multicenter, open-label, prospective randomized trial conducted by 20 surgeons from 13 tertiary hospitals. The trial protocol was published previously[12] and approved by the institutional review board of each participating site. An independent data and safety monitoring committee monitored the trial safety and progress. The trial was overseen by a steering committee (Data Supplement).

Patients

The trial enrolled patients with gastric cancer suitable for curative resection by distal subtotal gastrectomy. Patients were 20-80 years old; had an Eastern Cooperative Oncology Group performance status score of 0 or 1, an American Society of Anesthesiologists class of I-III, and primary gastric carcinoma with clinical stage T2-4a and no nodal metastasis or limited perigastric nodal metastasis in the preoperative studies; and provided written informed consent before participation. The exclusion criteria were possible distant metastasis detected in the preoperative studies, past history of gastric resection, gastric cancer–related complications, history of chemotherapy or radiotherapy for gastric cancer, other malignancy diagnosed within the previous 5 years, presence of vulnerable conditions (eg, cognitive impairment, ongoing or planned pregnancy), and current or past participation in another clinical trial within the past 6 months.

Objectives and End Points

The primary end point was to evaluate the noninferiority of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer compared with open surgery in terms of the 3-year relapse-free survival rate, which was calculated from the date of surgery to the date of recurrence detection or death from any cause. The secondary objectives included comparing the postoperative morbidity and mortality, postoperative recovery, quality of life, and 3-year overall survival between the two groups.

Randomization and Masking

A Web-based registration system was used to control and balance the treatment arms and total sample size. The system provided an allocation number with a pregenerated randomized code to all patients. The patients were allocated in order of the enrollment day. A randomized block design in a 1-to-1 allocation ratio was applied for randomization with each surgeon as the stratification factor to minimize the bias caused by the surgeons' technical proficiency. To maintain the properties of randomization, the block size was not open to the investigators. Surgeons were immediately notified of the randomization results via e-mail, and surgeons informed their patients regarding the type of operation they would undergo. Therefore, masking treatment allocation to the surgeons and patients was not possible as a result of the nature of the surgical clinical trial.

Surgical Quality Control, Procedures, and Follow-Up

Before initiating the trial, a separate study (KLASS-02-QC) was conducted to qualify surgeons with appropriate surgical skills; this was based on a standardized protocol for each surgical procedure.[14] The detailed criteria for the

participating surgeons in KLASS-02-QC and the procedures for KLASS-02-RCT have been described previously.[12,14] To participate in the trial, the surgeons and hospitals had to meet the following criteria: surgeons had to have performed > 100 gastrectomies for gastric cancer (including 50 cases each of laparoscopic and open gastrectomy) and hospitals had to have an annual volume of > 80 gastrectomies. In both approaches, standard radical distal gastrectomy with D2 lymphadenectomy with total omentectomy was performed.[14] Dissection of 14v lymph nodes was optional. The reconstruction method was decided according to each surgeon's preference. Adjuvant chemotherapy (S-1 monotherapy or oxaliplatin plus capecitabine) was recommended for all patients with pathologic stage II or greater advanced disease.

After surgery, the patients were followed regularly with the same protocol, and data, including recurrence and death, were recorded. Follow-up was conducted every 3 months for the first 2 years postoperatively and every 6 months for the next 3 years.[12] To assess the 3-year relapse-free survival rate, the criteria for recurrence were outlined in detail. In patients without specific symptoms, recurrence was detected on regular follow-up investigations, such as abdominopelvic computed tomography (CT). If the results were suspicious, whole-body positron emission tomography-CT, magnetic resonance imaging of the liver, or laparoscopic exploration was performed to confirm recurrence. Otherwise, the patients attended follow-up visits at shorter intervals than the planned schedule. Patients with specific symptoms, such as abdominal mass, weight loss, or obstruction, that may develop concurrently with recurrence were evaluated, regardless of their follow-up schedule.

Statistical Analysis

The effective sample size was calculated based on a 3-year relapse-free survival rate of 72% for patients with locally advanced gastric cancer undergoing open subtotal gastrectomy with D2 lymphadenectomy plus adjuvant chemotherapy, based on the results of a previous study.[15] The hypothesis was tested using Cox regression analysis, which revealed that the 3-year relapse-free survival rate of laparoscopic gastrectomy would be noninferior to that of open gastrectomy with a hazard ratio (HR) of 1.43 as the noninferiority margin (corresponding to an 8% 3-year relapse-free survival rate margin). To prove the noninferiority at 90% power for a one-sided α of 2.5% using the log-rank test, the sample size was calculated as 850 patients (425 patients per group), and the total number of target events was calculated as 330. A total of 1,050 patients (525 patients per group) was estimated to allow for a dropout rate of 10% after randomization. We planned to analyze the primary end point on a full analysis set basis. Patients who crossed over to a different treatment preoperatively were considered to belong to the group to which they crossed over (ie, actual surgical procedure performed) for an as-treated analysis of the full analysis set. However, patients who converted from laparoscopic to open surgery intraoperatively were grouped in the laparoscopic group.

All the statistical analyses were conducted using the R version 3.5.3 (R Foundation for Statistical Computing). χ^2 or Fisher's exact tests and the *t* test or Mann-Whitney *U* test were used for statistical analysis, as appropriate. Kaplan-Meier curves were used to estimate the overall and relapse-free survival. The HR and two-sided 95% CIs were estimated using a Cox regression model after confirmation of the proportional hazards assumption.

RESULTS

Patients

From November 2011 to April 2015, 1,050 patients with locally advanced gastric adenocarcinoma were recruited. Of these, 524 patients were randomly assigned to laparoscopic surgery and 526 were assigned to open surgery. After randomization, 39 patients (laparoscopy, n = 16; open surgery, n = 23) who did not undergo gastrectomy were excluded. Thirty-seven patients (laparoscopy, n = 21; open surgery, n = 16), including those who underwent R1 or R2 resection, were lost to follow-up, or experienced operative mortality, were excluded because it was not possible to evaluate the their 3-year relapse-free survival. Seventeen patients (laparoscopy, n = 11; open surgery, n = 6) underwent surgery via an approach opposite to the one to which they were assigned; these patients were reassigned to the group that corresponded to the surgery undergone according to the analysis plan. Thus, the full analysis set included 974 patients (492 in the laparoscopic group and 482 in the open group; Fig 1). The two study groups were balanced with respect to the baseline clinical characteristics (Table 1).

Operative and Pathologic Outcomes

Previously, we reported the operative and pathologic outcomes in detail, although there were minor differences between patients included in this analysis and those in the previous study.[13] Laparoscopic surgery was converted to open surgery in 12 patients (2.4%) for oncologic reasons, such as severe extension of tumors in nine patients, uncontrollable bleeding on laparoscopy in two patients, and a severe comorbidity in one patient who could not tolerate pneumoperitoneum. According to the analysis plan, these patients were included in the laparoscopy group. All patients in the laparoscopy group underwent D2 lymphadenectomy, whereas three patients (0.6%) in the open group underwent lymphadenectomy less than D2. The laparoscopy group showed a significantly higher incidence of gastrojejunostomy and longer operation time ($P < .001$ for both) but significantly less blood loss than the open group. Other operation details were similar in both groups. Bowel function recovery was significantly faster in the laparoscopy group than in the open group (3.5 *v* 3.7 days, respectively;

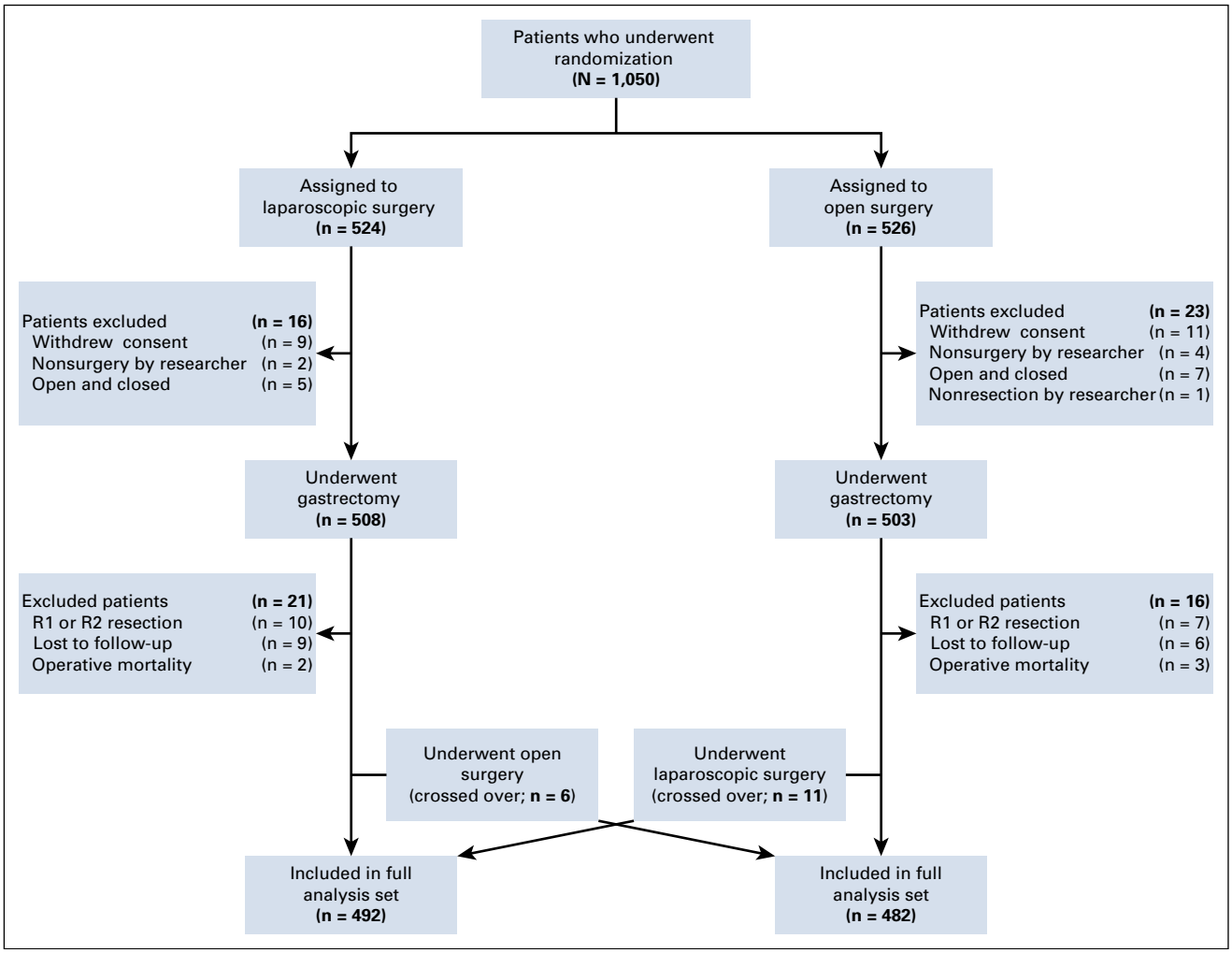

FIG 1. Trial profile. Nonsurgery by researcher, the patient did not undergo surgery by researcher's decision; open and closed, after opening the abdomen, the researcher closed the abdomen without any surgery; nonresection by researcher, the patient underwent surgery such as bypass, not gastrectomy.

P = .0431). The mean hospital stay was significantly shorter for the laparoscopy group than for the open group (8.0 *v* 9.1 days, respectively; P = .0047).

The mean number of retrieved lymph nodes, proportion of patients with < 16 retrieved lymph nodes, and pathologic TNM stage were similar in both groups. T1 tumors were detected in both groups, although they were diagnosed clinically as T2 or higher stage tumors (laparoscopy, 27.8%; open surgery, 25.9%; Table 2).

The laparoscopy group suffered fewer early postoperative complications than the open surgery group (15.7% *v* 23.4%, respectively; P = .0027), especially local complications such as intra-abdominal fluid collection and bleeding. The laparoscopy group experienced fewer complications during follow-up compared with the open group (4.7% *v* 9.5%, respectively; P = .0038), particularly intestinal obstruction (2.0% *v* 4.4%, respectively; P = .0447; Table 3). Clavien-Dindo grade III or higher complications were more frequent in the open surgery group (11.6%) than in the laparoscopy group (8.1%), although the difference was not statistically significant (P = .5812).

The rates of postoperative adjuvant chemotherapy were similar in both groups (laparoscopy, 60.6%; open surgery, 62.0%). There were no significant between-group differences regarding the chemotherapy regimen type, completion rate of adjuvant chemotherapy, or time to adjuvant chemotherapy initiation (Data Supplement).

Survival Outcomes

After a median follow-up time of 36.3 months, 45 patients (9.1%) in the laparoscopy group and 45 patients (9.3%) in the open surgery group died. The 3-year overall survival rates for the laparoscopy and open surgery groups were 90.6% (95% CI, 88.0% to 93.2%) and 90.3% (95% CI, 87.6% to 93.0%; log-rank P = .961; Data Supplement), respectively. The number of deaths or recurrences was 85 (17.3%) in the laparoscopy group, whereas it was 80 (16.6%) in the open surgery group. The 3-year relapse-free survival rates for the laparoscopy and open groups were 80.3% (95% CI, 76.0% to 85.0%) and 81.3% (95% CI,

TABLE 1. Patient Baseline Clinical Characteristics

Characteristic	Laparoscopy (n = 492)	Open Surgery (n = 482)	P
Mean age, years (SD)	59.8 (11.0)	59.4 (11.5)	.6203
Sex			.5743
Men	351 (71.3)	335 (69.5)	
Women	141 (28.7)	147 (30.5)	
Mean body mass index, kg/m^2 (SD)	23.5 (2.9)	23.7 (3.3)	.2035
ASA class			.9339
I	239 (48.6)	235 (48.8)	
II	228 (46.3)	225 (46.7)	
III	25 (5.1)	22 (4.6)	
Clinical T stage			.8411
T2	209 (42.5)	200 (41.5)	
T3	186 (37.8)	191 (39.6)	
T4a	97 (19.7)	91 (18.9)	
Clinical N stage			.4375
N0	218 (44.3)	201 (41.7)	
N+	274 (55.7)	281 (58.3)	
Clinical TNM stage			.6340
I	134 (27.2)	116 (24.1)	
IIA	75 (15.2)	84 (17.4)	
IIB	84 (17.1)	85 (17.6)	
III	199 (40.4)	197 (40.9)	

NOTE. Values are No. patients (%), unless otherwise indicated.

Abbreviations: ASA, American Society of Anesthesiologists; SD, standard deviation.

77.0% to 85.0%; log-rank $P = .726$; Fig 2), respectively. In the intent-to-treat population, the 3-year relapse-free survival rates for the laparoscopy and open groups were 77.8% (95% CI, 73.3% to 82.3%) and 80.0% (95% CI, 75.8% to 84.1%; log-rank $P = .489$; Data Supplement), respectively. Because randomization was performed with each surgeon as the stratification factor, the HR was calculated after adjusting for surgeon stratification. The HR for relapse-free survival, after adjusting for surgeon stratification using a Cox regression model, in the laparoscopy group compared with the open group was 1.035 (95% CI, 0.762 to 1.406; log-rank $P = .827$; P for noninferiority = .039). Further analysis using a Cox regression model when stratified by pathologic stage showed that the HR was 1.020 (95% CI, 0.751 to 1.385; log-rank $P = .900$; P for noninferiority = .030).

Recurrence was recorded in 76 patients (15.4%) in the laparoscopy group and 72 patients (14.9%) in the open surgery group; this difference was not statistically significant ($P = .78$). The recurrence patterns for both groups were similar. Among patients with mixed recurrence, peritoneal recurrence was most common in both groups (laparoscopy, n = 40 [8.1%]; open, n = 37 [7.8%]; $P = .48$), whereas 10 laparoscopy patients (2.0%) and 15 open surgery patients (3.1%) experienced locoregional recurrence ($P = .60$; Data Supplement). Post hoc subgroup analysis of relapse-free survival in the full analysis set revealed no significant interaction between treatment effects and any baseline clinical findings, including body mass index (Data Supplement).

DISCUSSION

The KLASS-02-RCT proved that the relapse-free survival of laparoscopic distal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer is noninferior to that of open gastrectomy at 3 years postoperatively. After adjusting for pathologic stage, relapse-free survival outcomes of laparoscopy are noninferior to those of open gastrectomy. The actual between-group difference in relapse-free survival was acceptably small for clinical application. Recurrence rates and patterns after laparoscopy were similar to those after open surgery.

Although laparoscopic surgery for locally advanced gastric cancer is common clinical practice worldwide, its oncologic safety has been questioned as a result of a potentially increased risk of locoregional and peritoneal recurrence. Unlike for early gastric cancer, laparoscopic gastrectomy for locally advanced gastric cancer is technically more difficult as a result of the difficulty in adequately manipulating the cancerous tissue during D2 lymphadenectomy based on the oncologic principle compared with open gastrectomy.[16] In the current trial, locoregional recurrence was lower in the laparoscopy group (2.0%) than in the open group (3.1%), although this difference was not statistically significant. Because peritoneal recurrence is the most common recurrence pattern, CO_2 pneumoperitoneum raises the concern of recurrence at wound and trocar sites as a result of a possibility of exaggerating tumor cell growth or dissemination.[17,18] Moreover, because of the lack of evidence from well-designed randomized trials, many treatment guidelines recommend open gastrectomy as the standard treatment of locally advanced gastric cancer.[1,19] However, in this trial, the peritoneal recurrence rate was similar in both groups. Therefore, these results indicate the oncologic safety of laparoscopic gastrectomy, when performed properly.

To our knowledge, this study is the first large-scale multicenter randomized trial designed and started to compare the surgical and oncologic safety of laparoscopic versus open gastrectomy for locally advanced gastric cancer, although similar studies were started in Eastern countries just after enrollment of the current study commenced.[10,11] The findings presented herein are parallel with those of recent large-scale retrospective and prospective studies that compared survival outcomes of laparoscopic and open gastrectomy.[20,21] The results of a recent randomized trial from China showed the noninferiority of laparoscopic distal gastrectomy, similar to our results.[11] Although the study

TABLE 2. Operative and pathologic data

Variable	Laparoscopy (n = 492)	Open Surgery (n = 482)	*P*
Mean incision length, cm (SD)	4.9 (2.5)	17.6 (3.2)	< .001
Mean operation time, minutes (SD)	227.0 (67.9)	164.4 (45.8)	< .001
Mean blood loss, mL (SD)	152.4 (260.5)	225.0 (211.5)	< .001
Extent of resection			.6975
Distal gastrectomy	477 (97.0)	470 (97.5)	
Total gastrectomy	15 (3.0)	12 (2.5)	
Extent of lymphadenectomy			.1208
< D2	0 (0.0)	3 (0.6)	
D2	492 (100.0)	479 (99.4)	
Anastomosis			< .001
Billroth I	175 (35.6)	278 (57.7)	
Billroth II	265 (53.9)	153 (31.7)	
Roux-en-Y	52 (10.6)	51 (10.6)	
Mean gas passing, days (SD)	3.5 (1.1)	3.7 (1.3)	.0431
Mean postoperative hospital stay, days (SD)	8.0 (6.3)	9.1 (6.3)	.0047
Mean tumor size, cm (SD)	4.6 (2.5)	4.6 (2.3)	.7797
Mean No. of retrieved lymph nodes (SD)	46.8 (18.0)	47.2 (16.2)	.6925
≥ 16 nodes	490 (99.6)	481 (99.8)	> .9999
< 16 nodes	2 (0.4)	1 (0.2)	
Mean No. of metastatic lymph nodes (SD)	3.5 (6.1)	3.4 (5.7)	.6382
Histology			.2617
Differentiated	197 (40.0)	187 (38.8)	
Undifferentiated	286 (58.1)	278 (57.7)	
Other	9 (1.8)	17 (3.5)	
Pathologic T stage			.7319
T1	137 (27.8)	125 (25.9)	
T2	104 (21.1)	113 (23.4)	
T3	132 (26.8)	135 (28.0)	
T4	119 (24.2)	109 (22.6)	
Pathologic N stage			> .9999
N0	223 (45.3)	219 (45.4)	
N+	269 (54.7)	263 (54.6)	
Pathologic TNM stage (eighth edition)			.3109
I	178 (36.2)	165 (34.2)	
II	148 (30.1)	167 (34.6)	
III	166 (33.7)	150 (31.1)	

NOTE. Values are No. of patients (%) unless otherwise indicated.
Abbreviation: SD, standard deviation.

design and patient eligibility criteria were almost identical for both studies, we set a noninferiority margin of 8%, which is narrower than the margin set by the Chinese study (10%), where the noninferiority of laparoscopic gastrectomy was proved with an even narrower noninferiority margin. In the Chinese trial, the morbidity and mortality rates were similar between the laparoscopic and open surgery groups. However, in our trial, the superiority of laparoscopic gastrectomy was confirmed, because we noted fewer early postoperative complications, especially local complications, such as intra-abdominal fluid collection and bleeding.

TABLE 3. Distribution of Early and Late Complications

Complication	No. of Patients (%)		*P*
	Laparoscopy (n = 492)	Open Surgery (n = 482)	
Total early complications	77 (15.7)	113 (23.4)	.0027
Local complications	56 (11.4)	80 (16.6)	.0208
Wound	23 (4.7)	29 (6.0)	.3936
Intra-abdominal fluid collection	11 (2.2)	23 (4.8)	.0359
Intra-abdominal bleeding	1 (0.2)	8 (1.7)	.0198
Intraluminal bleeding	2 (0.4)	2 (0.4)	> .9999
Ileus	8 (1.6)	15 (3.1)	.1432
Anastomotic stricture	0 (0.0)	2 (0.4)	.2446
Anastomotic leakage	9 (1.8)	5 (1.0)	.4209
Pancreatitis/pancreatic leakage	9 (1.8)	3 (0.6)	.1438
Systemic complications	17 (3.5)	22 (4.6)	.4163
Pulmonary	12 (2.4)	15 (3.1)	.5627
Urinary	4 (0.8)	3 (0.6)	> .9999
Renal	1 (0.2)	0 (0.0)	> .9999
Hepatic	1 (0.2)	4 (0.8)	.2131
Cardiac	0 (0.0)	1 (0.2)	.4949
Endocrine	0 (0.0)	0 (0.0)	Not applicable
Other	14 (2.8)	18 (3.7)	.4758
Total late complications	23 (4.7)	46 (9.5)	.0038
Intestinal obstruction	10 (2.0)	21 (4.4)	.0447
Stenosis	0 (0.0)	0 (0.0)	Not applicable
Fluid collection or abscess	3 (0.6)	2 (0.4)	> .9999
Delayed gastric emptying	1 (0.2)	4 (0.8)	.2131
Reflux symptoms	0 (0.0)	3 (0.6)	.1208
Postgastrectomy symptoms	3 (0.6)	3 (0.6)	> .9999
Chronic wound complications	3 (0.6)	7 (1.5)	.2198
Other	5 (1.0)	8 (1.7)	.4164
Clavien-Dindo complication grade			.5812
I or II	51 (10.4)	83 (17.2)	
≥ III	40 (8.1)	56 (11.6)	

The expected number of events during the 3-year follow-up was 330; however, only 165 events occurred, suggesting that the survival of patients with stage II and III disease was better than that in the reference study. Moreover, compared with the Chinese study, our study population comprised more patients with early-stage disease (> 35% of patients with stage I disease), and more patients received adjuvant chemotherapy. In addition, the Chinese study included patients with stage IV disease, whereas we analyzed only patients who had undergone curative resection. These differences probably contributed to the higher survival rate reported in our study, although the inclusion criteria of our study were similar to those of the Chinese study.

Laparoscopy was associated with less estimated blood loss, shorter hospital stays, and fewer postoperative complications in the short and long term. Together with better surgical outcomes and minimal invasiveness, fewer long-term postoperative complications in the laparoscopy group in this study strongly support the adoption of laparoscopic distal gastrectomy as a standard alternative treatment of locally advanced gastric cancer.

This study maintained the quality of the trial by using hospital and surgeon volumes as eligibility criteria and by evaluating the technical proficiency of the surgeons. To the best of our knowledge, this is the first surgical trial to evaluate the surgeons' skill before conducting the trial by reviewing unedited videos of both laparoscopic and open gastrectomy with D2

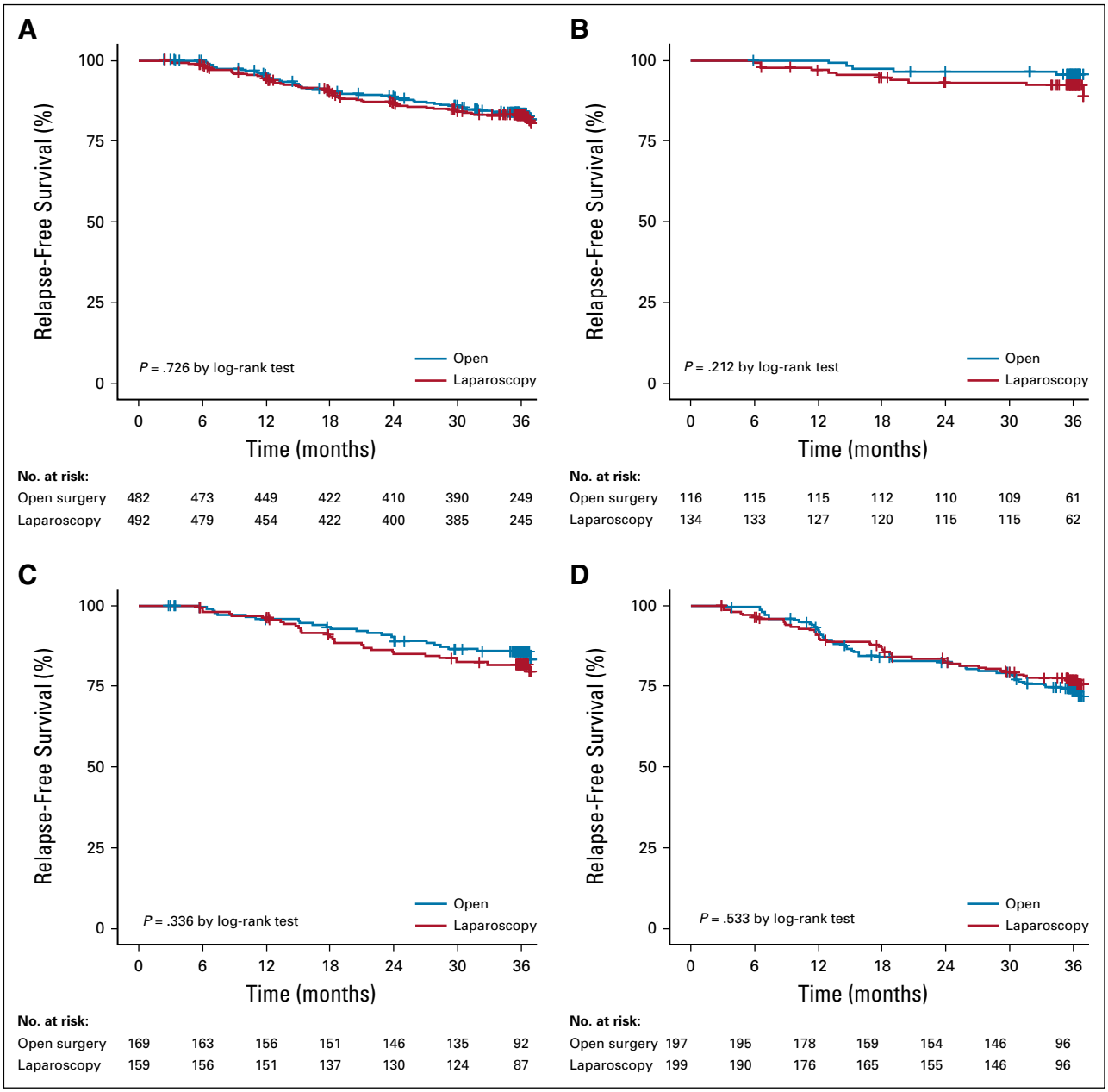

FIG 2. Kaplan-Meier curves comparing relapse-free survival between laparoscopic gastrectomy and open gastrectomy in (A) all patients and patients with (B) stage I, (C) stage II, and (D) stage III gastric cancer.

lymphadenectomy.[14] It is well proven that surgical proficiency improves survival rates and reduces the incidence of postoperative complications after gastrectomy.[22-24] We report satisfactory surgical and better postoperative outcomes after laparoscopic surgery. In addition, the mean number of patients enrolled in our trial was sufficiently large (80.8 patients per hospital; 23.6 patients per hospital per year) to guarantee good-quality data, high compliance with study protocol, and extremely low rates of follow-up loss.

The trial has several limitations. More than 35% of the study population was composed of patients with stage I cancer, although this was inevitable considering the overestimation probability of preoperative evaluation. A study population that was relatively younger than that in the reference study may have resulted in the smaller number of events than expected. Application of laparoscopy for total gastrectomy or after neoadjuvant treatment should be verified through other clinical trials. Accordingly, we are currently conducting a trial comparing laparoscopic total gastrectomy with open surgery for advanced upper gastric cancer and planning a trial of laparoscopic surgery after neoadjuvant chemotherapy for gastric cancer. Our results may not be generalizable to less experienced surgeons. However, considering the survival improvements after gastrectomy by

centralization,[23,24] performing laparoscopic surgery for locally advanced gastric cancer by a surgeon specialized in gastric cancer surgery is ideal. A small number of patients did not undergo the type of surgery to which they were randomly assigned (17 patients, 1.7%). Increasing interest in laparoscopic surgery among patients on initiation of the KLASS-02 trial may have influenced their decisions to change from open to laparoscopic surgery after randomization. The remaining patients wanted to undergo open surgery, which was recommended as a standard treatment by many guidelines. The 3-year follow-up time is relatively short considering the high survival rate; therefore, a study with longer-term follow-up is necessary.

In summary, this trial demonstrated that the 3-year relapse-free survival after laparoscopic distal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer is comparable to that of open surgery. The actual between-group difference in relapse-free survival was acceptably small for clinical application. Laparoscopic surgery was associated with a lower incidence of early and late postoperative complications and better postoperative recovery than open surgery. Therefore, this study supports use of laparoscopic distal gastrectomy with D2 lymphadenectomy as a potential standard treatment option for clinical locally advanced gastric cancer if the procedure is performed by qualified surgeons.

AFFILIATIONS

[1]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea
[2]Department of Surgery, Seoul National University Hospital, Seoul, Republic of Korea
[3]Department of Surgery, Chonnam National University Hwasun Hospital, Gwangju, Republic of Korea
[4]Department of Surgery, Yeouido St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea
[5]Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[6]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea
[7]Department of Surgery, Ajou University School of Medicine, Suwon, Republic of Korea
[8]Department of Surgery, Dong-A University Hospital, Korea, Busan, Republic of Korea
[9]Department of Surgery, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea
[10]Department of Surgery, Incheon St Mary's Hospital, The Catholic University of Korea, Incheon, Republic of Korea
[11]Center for Gastric Cancer, National Cancer Center, Goyang, Republic of Korea
[12]Department of Surgery, Yonsei University Gangnam Severance Hospital, Seoul, Republic of Korea
[13]Department of Surgery, Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

CORRESPONDING AUTHOR

Sang-Uk Han, MD, PhD, Department of Surgery, Ajou University School of Medicine, 206 Worldcup-ro, Yeongtong-gu, Suwon 443-749, Republic of Korea; e-mail: hansu@ajou.ac.kr.

SUPPORT

Supported by grants from the National R&D Program for Cancer Control, the Ministry of Health and Welfare, Republic of Korea (1320270), and Ethicon Endo-Surgery and by Johnson & Johnson Company and Jeil Pharmaceutical.

CLINICAL TRIAL INFORMATION

NCT01456598

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01210.

AUTHOR CONTRIBUTIONS

Conception and design: Woo Jin Hyung, Han-Kwang Yang, Young-Kyu Park, Hyuk-Joon Lee, Hyung-Ho Kim, Hoon Hur, Min-Chan Kim, Do Joong Park, Sang-Uk Han
Provision of study materials or patients: Hyuk-Joon Lee, Hyung-Ho Kim, Hoon Hur, Min-Chan Kim, Gyu Seok Cho, Jin-Jo Kim, Young Woo Kim, Jong Won Kim
Collection and assembly of data: Han-Kwang Yang, Young-Kyu Park, Hyuk-Joon Lee, Ji Yeong An, Wook Kim, Hyoung-Il Kim, Hyung-Ho Kim, Seung Wan Ryu, Hoon Hur, Min-Chan Kim, Seong-Ho Kong, Gyu Seok Cho, Jin-Jo Kim, Do Joong Park, Keun Won Ryu, Young Woo Kim, Jong Won Kim, Joo-Ho Lee, Sang-Uk Han
Data analysis and interpretation: Young-Kyu Park, Hyuk-Joon Lee, Hyung-Ho Kim, Do Joong Park, Keun Won Ryu, Young Woo Kim, Jong Won Kim, Sang-Uk Han
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the Korean Laparoendoscopic Gastrointestinal Surgery Study group for their support and the Clinical Trial Center of Ajou University Medical Center, which collected and analyzed the clinical data. In addition, the authors thank Dr Hyun Young Lee for her help with statistical analysis. We acknowledge the assistance of the Editage company for copyediting and correcting our use of the English language.

REFERENCES

1. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group and Review Panel: Korean practice guideline for gastric cancer 2018: An evidence-based, multi-disciplinary approach. J Gastric Cancer 19:1-48, 2019
2. Son T, Hyung WJ: Laparoscopic gastric cancer surgery: Current evidence and future perspectives. World J Gastroenterol 22:727-735, 2016
3. Deng Y, Zhang Y, Guo TK: Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: A meta-analysis based on seven randomized controlled trials. Surg Oncol 24:71-77, 2015

4. Kelly KJ, Selby L, Chou JF, et al: Laparoscopic versus open gastrectomy for gastric adenocarcinoma in the West: A case-control study. Ann Surg Oncol 22: 3590-3596, 2015
5. Kim W, Kim HH, Han SU, 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 263:28-35, 2016
6. Kim HH, Han SU, Kim MC, et al: 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 5:506-513, 2019
7. Kim YW, Baik YH, Yun YH, et al: Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: Results of a prospective randomized clinical trial. Ann Surg 248:721-727, 2008
8. Katai H, Sasako M, Fukuda H, et al: Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: A multicenter phase II trial (JCOG 0703). Gastric Cancer 13:238-244, 2010
9. Volz J, Köster S, Spacek Z, et al: The influence of pneumoperitoneum used in laparoscopic surgery on an intraabdominal tumor growth. Cancer 86:770-774, 1999
10. Inaki N, Etoh T, Ohyama T, et al: A multi-institutional, prospective, phase II feasibility study of laparoscopy-assisted distal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer (JLSSG0901). World J Surg 39:2734-2741, 2015
11. Yu J, Huang C, Sun Y, et al: Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: The CLASS-01 randomized clinical trial. JAMA 321:1983-1992, 2019
12. Hur H, Lee HY, Lee HJ, et al: Efficacy of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer: The protocol of the KLASS-02 multicenter randomized controlled clinical trial. BMC Cancer 15:355, 2015
13. Lee HJ, Hyung WJ, Yang HK, et al: 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 270:983-991, 2019
14. Kim HI, Hur H, Kim YN, et al: Standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC): A prospective, observational, multicenter study [NCT01283893]. BMC Cancer 14:209, 2014
15. Sakuramoto S, Sasako M, Yamaguchi T, et al: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810-1820, 2007
16. Memon MA, Khan S, Yunus RM, et al: Meta-analysis of laparoscopic and open distal gastrectomy for gastric carcinoma. Surg Endosc 22:1781-1789, 2008
17. Mathew G, Watson DI, Ellis TS, et al: The role of peritoneal immunity and the tumour-bearing state on the development of wound and peritoneal metastases after laparoscopy. Aust N Z J Surg 69:14-18, 1999
18. Mutter D, Hajri A, Tassetti V, et al: Increased tumor growth and spread after laparoscopy vs laparotomy: Influence of tumor manipulation in a rat model. Surg Endosc 13:365-370, 1999
19. Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 20:1-19, 2017
20. Kim HH, Han SU, Kim MC, et al: Long-term results of laparoscopic gastrectomy for gastric cancer: A large-scale case-control and case-matched Korean multicenter study. J Clin Oncol 32:627-633, 2014
21. Kinoshita T, Uyama I, Terashima M, et al: Long-term outcomes of laparoscopic versus open surgery for clinical stage II/III gastric cancer: A multicenter cohort study in Japan (LOC-A Study). Ann Surg 269:887-894, 2019
22. Smith JK, McPhee JT, Hill JS, et al: National outcomes after gastric resection for neoplasm. Arch Surg 142:387-393, 2007
23. Jensen LS, Nielsen H, Mortensen PB, et al: Enforcing centralization for gastric cancer in Denmark. Eur J Surg Oncol 36:S50-S54, 2010 (suppl 1)
24. Chan DS, Reid TD, White C, et al: Influence of a regional centralised upper gastrointestinal cancer service model on patient safety, quality of care and survival. Clin Oncol (R Coll Radiol) 25:719-725, 2013

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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

Han-Kwang Yang
Research Funding: Stryker

Hyung-Ho Kim
Research Funding: Olympus Korea

Hoon Hur
Honoraria: Johnson & Johnson Medical
Research Funding: AstraZeneca, Dong-A ST

Do Joong Park
Research Funding: Medtronic (Inst), Daewoong Pharmaceutical (Inst)

Jong Won Kim
Research Funding: Inframed, Donga-ST, Novomics

Sang-Uk Han
Research Funding: Jeil Pharmaceutical, Ethicon Endo-Surgery, Johnson & Johnson

No other potential conflicts of interest were reported.