Received: 1 June 2021 | Revised: 3 February 2022 | Accepted: 6 February 2022

DOI: 10.1002/ags3.12559

REVIEW ARTICLE

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

Minimally invasive surgery in advanced gastric cancer

Sangjun Lee[1] | **Hyung-Ho Kim**[1,2]

[1]Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Korea

[2]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

Correspondence
Hyung-Ho Kim, Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Korea, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, 13620, South Korea.
Email: lapakh2@gmail.com

Abstract

Since Dr. Kitano introduced laparoscopic distal gastrectomy for early gastric cancer in 1994, there have been remarkable advances in minimally invasive surgery (MIS) for gastric cancer, including robotic surgery. With the efforts of many clinical researchers and consenting patients, medical knowledge and evidence for laparoscopic surgery in gastric cancer have accumulated. Although many gastric surgeons are comfortable with the clinical application of laparoscopic surgery for early gastric cancer, the adoption of MISs for advanced gastric cancer remains controversial. In this review article, we describe the current status and evidence of MIS from an evidence-based medicine viewpoint and explore the feasibility and effectiveness of MIS for advanced gastric cancer in the real world.

KEYWORDS
advanced gastric cancer, borderline resectable gastric cancer, conversion surgery, minimally invasive surgery

1 | INTRODUCTION

Gastric cancer (GC) is one of the most common cancers worldwide. According to GLOBOCAN 2018, there were over 1 000 000 new cases of GC in 2018 and an estimated 783 000 deaths, making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide.[1] The traditional treatment option for GC is surgical resection, which includes gastrectomy with D2 lymph node dissection after laparotomy. However, several less invasive procedures and minimally invasive surgeries (MISs) have been developed to reduce the invasiveness of surgery and improve patients' quality of life. In 1994, Dr. Seigo Kitano first introduced laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer (EGC). Since then, based on many studies and clinical trials, the laparoscopic approach has become increasingly established in GC surgery.[2] In addition, even more popular than LADG, a totally laparoscopic gastrectomy technique has been developed to reduce surgical wound and surgical stress compared to laparoscopic-assisted methods. In 2009, Ikeda et al reported the advantages of totally laparoscopic distal gastrectomy (TLDG) over LADG as less invasive, secure ablation of the tumor with the stomach, and safe anastomosis.[3] Chen et al reported that TLDG had a longer surgery time but less bleeding and shorter hospitalization than open gastrectomy (OG) in a systematic review including one randomized controlled trial (RCT) and 13 observational studies.[4]

In eastern Asian countries, several study groups have been established as a platform to organize and conduct prospective RCTs in each country; for example, the Japanese Clinical Oncology Study Group (JCOG) in Japan, the Korean Laparoscopic Gastrointestinal Surgical Study Group (KLASS) in South Korea, and the Chinese Laparoscopic Gastrointestinal Surgical Study Group (CLASS) in China to evaluate the safety and feasibility of MIS on GC. In Korea, the KLASS-01 trial has proven the efficacy of laparoscopic distal gastrectomy (LDG) vs open subtotal gastrectomy for clinical stage I GC with better short-term outcomes and equivalent long-term survival.[5,6] In Japan, similar results have been demonstrated for LDG vs open distal gastrectomy for clinical stage IA/IB GC in the JCOG 0912 trial.[7,8] In China, the safety of laparoscopic total gastrectomy

(LTG) for clinical stage I GC over open total gastrectomy (OTG) was demonstrated in the CLASS02 trial.[9]

By virtue of these studies (Table 1), LDG has been widely used and accepted for EGC. It has been adopted as one of the treatment options in general practice for clinical stage I GC according to the Japanese Gastric Cancer Treatment Guidelines (v. 5)[10] and the Korean Practice Guidelines for Gastric Cancer, 2018.[11] According to the Korean guidelines, laparoscopic gastrectomy (LG) is recommended for EGC because of its smoother and faster postoperative recovery, fewer complications, better quality of life, and equivalent long-term survival than OG. In EGC in the upper third, both laparoscopic proximal gastrecomy and LTG can be safe and feasible without compromising short-term and long-term outcomes.[12,13] The operation method would be selected considering the survival rate, nutritional status, and quality of life.

Although there is no disagreement on the clinical application of MIS in patients with EGC, controversy remains regarding the implementation of MIS for advanced gastric cancer (AGC) despite the results of a few phase III studies. This review examines the current status and evidence of MIS for AGC. It discusses the role of laparoscopic surgery in a more advanced clinical stage, which is still an unexplored field.

2 | MINIMALLY INVASIVE SURGERY IN RESECTABLE ADVANCED GASTRIC CANCER

Although MIS is one of the standard treatment options for EGC, the standard treatment for AGC is OG with D2 lymph node dissection,[10] so far in the guidelines due to lack of enough solid evidence. However, the clinical results on the safety and long-term outcomes of laparoscopic GC surgery are increasingly convincing through several well-designed RCTs and large-scale retrospective studies. Kim et al retrospectively analyzed the long-term oncologic outcomes of 2976 patients who had been treated with radical gastrectomy with curative intent, either LG or OG.[14] After propensity score matching, the overall survival rate (OSR), disease-specific survival, and recurrence-free survival rates were not significantly different between LG and OG for each cancer stage. Therefore, the authors concluded that the long-term oncologic results for laparoscopic procedures were the same as those for open radical gastrectomy.

For distal gastrectomy, some large-scale RCTs have verified the safety and feasibility of the laparoscopic approach over OG. The CLASS-01 trial from China first addressed the noninferiority of LDG with lymph node dissection compared to standard OG in 3-y disease-free survival rate (DFSR).[15] In that trial, 1056 patients with clinical T2-4aN0-3M0 were enrolled and randomly assigned to the laparoscopic and open groups (N = 528 per group). The primary outcome was the 3-y DFSR, which was comparable between the two groups in the primary analysis population (76.5% vs 77.8%, 1-sided 97.5% confidence interval [CI]: −6.5% to ∞), per-protocol population (77.6% vs 78.5%, 1-sided 97.5% CI: −6.1% to ∞), and as-treated population (77.7% vs 78.4%, 1-sided 97.5% CI: −6.0% to ∞). Moreover, the

TABLE 1 Current status of randomized controlled trials for distal gastrectomy in early gastric cancer

Trial	Country	Study arms	Primary endpoint	Secondary endpoints	Recruitment	Main results
KLASS01 Phase III	Korea	LDG vs ODG in EGC	5-y OSR Noninferiority margin of −5%	Gastric cancer-specific survival, morbidity and mortality, quality of life, and cost-effectiveness	2006–2011 (N = 1416)	Comparable 5-y OSR of LDG vs ODG (94.2% vs 93.3%, $P = .64$) Comparable cancer-specific survival of LDG vs ODG (97.1% vs 97.2%, $P = .91$) Lower overall complication rate in LDG (13.0% vs 19.9%, $P = .001$)
JCOG 0912 Phase III	Japan	LDG vs ODG in EGC	5-y RFSR Noninferiority margin of a hazard ratio of 1.54.	5-y OSR, the proportion of LDG completion, proportion of conversion to open surgery, adverse events, short-term clinical outcomes, and postoperative quality of life	2010–2013 (N = 921)	Comparable 5-y RFSR of LDG vs ODG (94.0% vs 95.1%, (HR, 0.84 [90% CI, 0.56–1.27]), $P = .0075$) Comparable in-hospital grade 3–4 surgical complications (3.3% in LDG vs 3.7% in ODG)
CLASS02 Phase III	China	LTG vs OTG in EGC	Morbidity and mortality within 30 d following surgery Noninferiority margin of 10%	Recovery courses and postoperative hospital stays	2017–2018 (N = 227)	Comparable overall morbidity and mortality rates between the groups (19.1% vs 20.2%) Comparable overall postoperative complication rate (18.1% vs 17.4%)

Abbreviations: CI, confidence interval; EGCm, early gastric cancer; HR, hazard ratio; LDG, laparoscopic distal gastrectomy; LTG, laparoscopic total gastrectomy; ODG, open distal gastrectomy; OSR, overall survival rate; OTG, open total gastrectomy; RFSR, relapse-free survival.

3-y DFSR stratified by pathologic stage was similar between the two groups; for patients with stage I disease, 96.5% vs 91.3% (log-rank $P = .05$); for stage II, 87.5% vs 86.8% (log-rank $P = .89$); for stage III, 58.0% vs 63.8% (log-rank $P = .23$), and for stage IV, 20.8% vs 58.3% (log-rank $P = .13$). The postoperative morbidity rate was not significantly different between the two groups (15.2% in the laparoscopic group vs 12.9% in the open group, $P = .845$).[16] However, through a post-hoc analysis of the primary analysis population, excluding patients with pathologic stage I tumors (T1N0-1M0 and T2N0M0), the absolute difference in the 3-y DFSR was increased to −3.9% (1-sided 97.5% CI : −10.6% to ∞), which exceeded the prespecified noninferiority margin of −10%. This result indicated that many preoperative overstaged patients were enrolled in the primary dataset.

KLASS-02 from Korea has also proven the safety and efficacy of LDG with D2 lymphadenectomy for locally advanced GC in terms of comparable 3-y relapse-free survival rate (RFSR) and fewer postoperative complications.[17,18] In that trial, 1050 patients with clinical stage T2-4a and no nodal metastasis or limited perigastric nodal metastasis were randomly assigned to the laparoscopic (N = 524) and open groups (N = 526). After excluding patients who did not meet the eligibility criteria, the final datasets comprised 492 and 482 patients, respectively. The primary outcome of the study was the 3-y RFSR, which was comparable between the two groups: 80.3% (95% CI: 76.0%–85.0%) for the laparoscopic group vs 81.3% (95% CI: 77.0%–85.0%) for the open group (log-rank $P = -.726$). The noninferiority margin was 8%, which was narrower than that of the CLASS-01 trial. The early postoperative complication rate was significantly lower in the laparoscopic group than in the open group (15.7% vs 23.4%, $P = .0027$), especially for local complications (11.4% vs 16.6%, $P = .208$). Moreover, intraabdominal fluid collection and intraabdominal bleeding were significantly lower in the laparoscopic group (2.2% vs 4.8% for intraabdominal fluid collection, $P = .359$ and 0.2% vs 1.7% for intraabdominal bleeding $P = .0198$). The overall late complication rate was significantly lower in the laparoscopic group than in the open group (4.7% vs 9.5%, $P = .0038$). Intestinal obstruction was the most common late complication and was significantly less common in the laparoscopic group (2.0% vs 4.4%, $P = .0447$). Therefore, the authors concluded that LDG with D2 lymphadenectomy for locally AGC was equivalent to open surgery in the 3-y RFSR and was associated with a lower incidence of early and late postoperative complications and better postoperative recovery than open surgery. That study also included patients with EGC, more than 35% of the total enrolment, diagnosed as AGC preoperatively. The 3-y RFSRs stratified by TNM stage were analyzed; however, the RFSRs of patients with stage II and III disease showed no significant difference between the two groups ($P = .336$ in stage II, $P = .533$ in stage III). Moreover, the 3-y RFSR was ~75%, slightly higher than the 3-y DFSR of those in the CLASS-01 trial (63.8%).

One limitation of the abovementioned studies, although unavoidable, is the high number of patients with pathologic stage I who were enrolled. Almost one-third of the study population (laparoscopy and open: 29.2% and 29.3% in CLASS 01, 36.2% and 31.1% in KLASS 02) was stage I disease. Such a high proportion of patients with stage I disease will likely have affected the statistical power of these studies and reproducibility in other countries, especially the Western world. Furthermore, these two clinical trials were designed to assume that the 3-y RFSR had the same oncologic outcomes as the 5-y OSR.[19] Therefore, whether there is no difference in the oncological outcomes between laparoscopic surgery and open surgery could be verified with the final confirmation of the 5-y OSRs in these two study cohorts.

Inaki et al demonstrated the safety of LDG with D2 lymph node dissection for locally advanced GC in the JLSSG 0901 trial.[20] In this trial, 507 patients were enrolled and randomly distributed to the laparoscopic (N = 252) and open groups (N = 255). After excluding 47 ineligible patients, the laparoscopic group was associated with lower estimated blood loss (30 vs 150 mL, $P < .0001$), less analgesic use (38.3% vs 53.6%, $P = .0001$), shorter first day of flatus (2 vs 3 d, $P < .0001$), and longer operation time (291 vs 205 min, $P < .0001$). There were no significant differences in all Clavien–Dindo (CD) grade intraoperative complications (0.9% vs 2.6%, $P = .285$) and CD grade IIIa or higher postoperative complications (3.1% vs 4.7%, $P = .473$) between the two groups. A phase III trial to confirm the noninferiority of long-term outcomes of the laparoscopic procedure to OG has been ongoing in the same study population (UMIN Clinical Trials Registry number: UMIN000003420). Table 2 summarizes the milestone clinical trials of LDG for AGC.

In addition to these large-scale RCTs, a few meta-analyses have compared laparoscopic and open approaches for AGC. Zou et al conducted a meta-analysis consisting of one RCT and 13 non-RCTs; the analysis included a total of 2596 patients from 493 studies for patients with AGC based on PubMed, EMBASE, and Cochrane Library databases, filtered by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement.[21] In this meta-analysis, LG was associated with significantly less blood loss (weighted mean difference [WMD] −137.87 mL, 95% CI: −164.41 to −111.33. $P < .01$), less overall postoperative morbidity (odds ratio [OR] 0.78, 95% CI: 0.61-0.99, $P = .04$), and shorter postoperative hospitalization days (WMD −3.08 d, 95% CI: −4.38 to −1.78, $P < .001$), but longer operative time (WMD 57.06 min, 95% CI: 41.87 to 72.25, $P < .01$). There were no statistically significant differences between the two groups in terms of reoperation rate (hazard ratio [HR] 1.58; 95% CI: 0.58–4.31, $P = .37$), postoperative mortality (HR 0.69, 95% CI: 0.21–2.26, $P = .54$), harvested lymph node number (WMD −0.11, 95% CI: −2.72 to 2.5, $P = .94$), tumor recurrence rate (HR 0.79, 95% CI: 0.6–1.04, $P = .09$), 3-y DFSR (HR 1.02, 95% CI: 0.64–1.61, $P = .94$), and 5-y OS (HR 0.79, 95% CI: 0.46–1.34, $P = .38$). The authors concluded that LG might be a safe and effective treatment for locally AGC with some advantages over OG, although LG requires a longer operation time. Furthermore, other meta-analyses have reached the same conclusion that LDG is both safe and feasible and has advantages, including fewer postoperative complications.[22,23]

For total gastrectomy at the middle or upper third locally AGC, there is no RCT. The evidence mostly came from retrospective case-controlled studies. Jianjun Du et al compared 82 LTG with

TABLE 2 Current status of randomized controlled trials for distal gastrectomy in advanced gastric cancer

Trial	Country	Study arms	Primary endpoint	Secondary endpoints	Main results
CLASS01 Phase III	China	LDG vs ODG in AGC	3-y DFSR	3-y OSR, recurrence pattern	Comparable 3-y DFSR of LAG to ODG (76.5% vs 77.8%) Comparable postoperative complication rate of LDG to ODG (15.2% vs 12.9%, *P* = .845)
KLASS02 Phase III	Korea	LDG vs ODG in AGC	3-y RFSR	3-y OSR, morbidity and mortality, postoperative recovery index, and quality of life	Comparable 3-y RFS of LDG to ODG (80.3% vs 81.3%, *P* = .726) Significantly lower overall complication rate of LDG (4.7% vs 9.5%, *P* = .0038)
JLSSG0901 Phase III	Japan	LDG in AGC	5-y RFSR	5-y OSR, adverse events and short-term clinical outcomes	Comparable overall postoperative complications (3.1% vs 4.7%, *P* = .473) Long-term outcome to be published

Abbreviations: AGC, advanced gastric cancer; DFSR, disease-free survival rate; LDG, laparoscopic distal gastrectomy; ODG, open distal gastrectomy; OSR, overall survival rate; RFSR, relapse-free survival rate.

94 cases of OTG with D2 lymph node resections in AGC.[24] In that study, LTG was associated with less postoperative complications (9.8% vs 24.5%), less operative blood loss (156 vs 339 mL, *P* < .001), earlier postoperative recovery (*P* < .001), a similar number of lymph nodes (34.2 vs 36.4, *P* = .331), and a longer operation time (275 vs 212 min, *P* < .001). During a mean follow-up period of 22.5 mo, local recurrence and distant metastasis were comparable between the two groups (19 of 82 patients vs 23 of 94 patients). Lee et al demonstrated an acceptable major morbidity rate in LTG for AGC.[25] In that study, 94 patients who underwent LTG were retrospectively analyzed. The median operation time was 230 min, and the median number of retrieved lymph nodes was 60.5. Major postoperative morbidity or CD grade IIIa or higher occurred in nine patients (9.6%). After a median follow-up period of 12.77 mo, 13 of 94 patients experienced tumor recurrence. The authors concluded that LTG with D2 lymphadenectomy is applicable to AGC in terms of the acceptable rate of major morbidity in this study. Lee et al conducted a comparative study comparing LTG and OTG for the upper or middle third GC.[26] In that study, 84 patients were divided into the laparoscopic (N = 34) and open (N = 50) groups. The laparoscopic group was associated with comparable postoperative morbidity (16.0% vs 17.6%, *P* = .842) and marginal survival benefit in terms of the 5-y OSR (93.2% vs 77.5%, *P* = .082). The authors concluded that LTG is ontologically safe, with a comparable recurrence rate and OSR.

Oh et al conducted a meta-analysis comparing LTG and OTG for patients with EGC and AGC from 19 studies, 3943 patients based on Google Scholar, Medline, PubMed, Embase, and Cochrane library under the PRISMA guidelines.[27] Similar results as those of distal gastrectomy were found; LTG was associated with less blood loss (WMD −133.55 mL, 95% CI: −172.39 to −94.70, *P* < .0001), shorter postoperative hospital stay (WMD −3.18 d, 95% CI: −4.64 to −1.71, *P* < .001) lower postoperative complication rate (HR 0.73, 95% CI: 0.61–0.88, *P* < .001, less dissected lymph nodes number (WMD −2.15, 95% CI: −3.19 to −1.11, *P* < .001), but longer operative time (WMD 39.666 min, 95% CI: 25.46–53.85, *P* < .001). The 5-y OSR of the LTG group was comparable to that of OTG. The authors mentioned that fewer harvested lymph nodes had an insignificant impact on survival. Ongoing trials and future studies could help to clarify the impact of fewer retrieved lymph nodes.

There are several ongoing RCTs comparing the effectiveness and feasibility of LTG with OTG for the upper and middle AGC. However, it has a long way to go because the studies are still in the patient recruitment stage. A phase III clinical trial, KLASS-06 NCT03385018, comparing LTG with lymph node dissection with OTG for AGC will provide more concrete scientific evidence of LTG for AGC.

However, some surgeons are concerned about the rapid implementation of LTG without clear evidence of outcomes. Kodera et al[28] retrospectively analyzed the efficacy and feasibility of LTG using a nationwide registry database, the NCD, in Japan. The laparoscopic procedure showed a significantly higher readmission rate, reoperation rate, and anastomotic leakage rate (5.4% vs 3.6%, *P* < .01 in stage I / 5.7% vs 3.6%, *P* =.02 in stage II–IV) than open surgery in the real world. Therefore, they recommended that LTG should only be implemented by experienced and well-trained teams.[28]

A few meta-analyses studies composed of retrospective studies are available. In 2005, in Italy, Huscher Cristiano et al reported a single-center RCT comparing laparoscopic and open subtotal gastrectomy for distal GC with 59 patients.[29] The patients were randomized to open group (N = 29 and laparoscopic group N = 30). Although clinical-stage information was not available, 23 (79.2%) patients of the open group and 23 (76.7%) patients of the laparoscopic group were T2N0 or over according to the 1997 AJCC pTNM staging system. The mean number of lymph nodes retrieved was 33.4 ± 17.4 in the open group and 30.0 ± 14.9 in the laparoscopic group. The overall postoperative morbidity rate was 27.6% vs 23.3%. Overall 5-y OSR was 55.7% vs 54.8%, and the 5-y DFSR was 58.9% and 57.3% (*P* = not significant), although the stage-stratified results were not shown. From these results, the authors concluded that LG was safe and feasible compared with OG, and long-term survival outcomes of LG were comparable to those of open surgery.

Van der Veen et al recently published a phase III, multicenter in the Netherlands, prospective RCT, LOGICA trial (NCT02248519), comparing LG and OG in resectable gastric cancer (cT1-4a, N0-3b, M0).[30] In that trial, between 2015 and 2018, 227 patients were assigned to the laparoscopic group (N = 115) and open group (N = 112) after randomization. Most patients were diagnosed with pT2 or higher (79.6% vs 78.4%, *P* = .178). The median hospital stay, which was the primary endpoint of the trial, did not show a significant difference (7.0 d, IQR 5. –-9.00 vs 7.0 d, IQR 5.00–9.00, *P* = .343). LG was associated with a longer operation time, and less blood loss. 1-y OSR was similar between the two groups (76% v 78%, *P* = 5.74). The authors concluded that LG did not reduce the hospital stay compared with OG, although postoperative complications and oncological efficacy were comparable.

For an AGC-specific study, Umberto Bracale et al reported a multicenter retrospective study concerning LG in the Italian population with stage II and III AGC.[31] In that study, 366 patients were included and underwent either LTG or LDG. The authors concluded LG for AGC is feasible and safe in terms of short-term postoperative and long-term survival outcomes. The median operation time was 273.8 ± 114.9 min for LTG and 236.6 ± 99.1 for LDG. The median number of harvested lymph nodes was 25 ± 10 for the LTG and 27 ± 11 for the LDG. The median hospital stay was 15 ± 12 d in LTG and 12 ± 8 d in LDG. The overall 30-d postoperative complication rate was 8.7% in LTG and 18.6% in LDG. Mortality occurred in three cases with LDG, which were all due to heart failure.

3 | ROBOTIC SURGERY

Robotic surgery, represented by the da Vinci system (Intuitive Surgical, Sunnyvale, CA, USA), has a few theoretical advantages over laparoscopic surgery. A so-called endo-wrist feature can provide an additional degree of freedom to a surgeon. Second, there is little instability from any hand trembling. Third, the existence of a third arm can reduce the need for assistance by human resources. Also, there are disadvantages of robotic surgery. The cost of robotic surgery is much more expensive than laparoscopic surgery. Third, the operation time is longer, mainly due to docking and undocking the main body from the surgical table and changing the surgical instrument. For gastrectomy, the features mentioned above may also be no exception.

Uyama et al conducted a phase II, multicenter, single-arm, prospective study comparing safety, feasibility, and the effectiveness of robotic gastrectomy (RG) using the da Vinci surgical system for patients with clinical stage I or II GC.[32] Between October 2014 and December 2016, 330 patients were enrolled, and 326 patients completed the trial protocol. Thirty-day postoperative morbidity rate over C-D grade IIIa was the primary endpoint. The same complication of conventional LG was a historical control. They hypothesized that the complication rate over C-D IIIa of RG could be reduced to half LG (6.4%), which was less than 3.2% as a threshold. The C-D grade IIIa or higher complication rate was 2.45%, which was significantly lower than the threshold (RR 0.9755, 95% CI: 0.9522 to 0.9893). There was no 30-d mortality. When compared to historical control, RG was associated with less blood loss (20 vs 37 mL, $P < .001$) and shorter hospital stay after the operation (9 vs 13 d, $P < .001$). The total operation time was similar between the two groups (313 vs 316 min, *P* = .837). The authors concluded that RG might be safe and feasible for treating GC in reduced severe morbidity that required any interventional treatment.

Recently published articles demonstrated the noninferiority of RG for GC compared with LG from several studies. However, most studies failed to figure out the theoretical advantages of RG over LG. Guerrini et al conducted a systematic review comprised of 7200 patients from nine observational studies for comparing RG to LG and OG in terms of short-term outcomes.[33] All the robotic surgeries included in that study utilized the da Vinci surgical system and were published since 2010. RG was associated with less blood loss (WMD −154.18 mL, 95% CI: −250.11 to −58.25, *P* = .006) and a shorter hospital stay (WMD −2.18 d, 95% CI: −2.81 to −1.54, *P* = < .001) than OG. Compared with LG, however, RG did not show any significance in blood loss (WMD −6.08 mL, 95% CI: −25.73 to 13.58, *P* = .54) and hospital stay(WMD −0.60 d, 95% CI: −1.39 to 0.20, *P* = .14). For the number of retrieved lymph nodes, RG was comparable to LG (WMD −0.25, 95% CI: −3.72 to 3.22, *P* = .89) and OG (WMD −1.13, 95% CI −2.47 to 0.21, *P* = .10). RG was associated with a comparable complication rate for both LG (OR 1.12, 95% CI 0.83–1.52, *P* = .44) and OG (OR 1.37, 95% CI: 0.92–2.06, *P* = .12). On the other hand, RG was associated with a longer operation time compared with both LG (WMD 61.99 min, 95% CI: 43.12–80.86, $P < .001$) and OG (WMD 65.73 min, 95% CI: 25.30–106.16, *P* = .001). For the cost-analysis, RG cost more than LG by €3189 per patient. The authors concluded in this systematic review that RG could have a comparable outcome as LG. However, the article included patients mainly with stage I GC. The further development of the robotic system and technique should focus on reducing the operation cost and operation time and proving the efficacy in terms of long-term survival outcomes.

4 | MINIMALLY INVASIVE SURGERY IN UNRESECTABLE OR BORDERLINE RESECTABLE GASTRIC CANCER

4.1 | Palliative surgery

According to the latest Japanese treatment guidelines, noncurative surgery can be offered to incurable patients to alleviate symptoms. Surgery to relieve symptoms may then be considered an option; either palliative gastrectomy or gastrojejunostomy (GJ) could be selected, depending on the resectability of the primary tumor and surgical risks.[10] Although gastrectomy plus chemotherapy has failed to prove a survival benefit over chemotherapy alone in the REGATTA trial,[34] there are still several positives regarding the survival benefit of the reduction surgery for stage IV GC. Min et al compared laparoscopic and open radical gastrectomy with maximum metastasectomy in patients with stage IV GC.[35] The authors implied that radical gastrectomy with maximum metastasectomy could have a potential role in stage IV GC. After comparing those who underwent the gastrectomy plus chemotherapy group in the REGATTA trial with those who met the criteria of the REGATTA trial in this study cohort, the 2-y OSR and mean survival time was 55.6%, and 26.8 mo, which was twice as high as those of the REGATTA trial (25.1% and 14.3 mo, respectively); this discrepancy can be attributed to the extent of surgery. The REGATTA trial only allowed limited surgical resection without metastasectomy. The authors suggested that LG with metastasectomy is safe and feasible for very selected stage IV patients and has comparable survival and fewer postoperative complications than open surgery.

In gastric outlet obstruction, laparoscopic bypass GJ can help patients resume food intake. Navarra et al conducted an RCT with a small number of patients (N = 24) comparing laparoscopic and open GJ for patients with gastric outlet obstruction.[36] The authors concluded that laparoscopic GJ was a safe, feasible, and an effective alternative to open GJ with less blood loss and shorter time to oral solid food intake. A comparative study by Ojima et al compared laparoscopic and open GJ in patients with gastric outlet obstruction (N = 53).[37] The authors also concluded that laparoscopic GJ was a valuable and feasible alternative to open GJ, with a lower postoperative delayed gastric emptying and shorter time to resume oral feeding.

5 | CONVERSION SURGERY AFTER NEOADJUVANT CHEMOTHERAPY

Several chemotherapy regimens have been developed to improve the survival of patients with stage IV GC. In addition to palliative chemotherapy or palliative surgery, new therapeutic approaches should be considered to enhance the survival of patients with stage IV GC. Several conversion therapeutic approaches have been successfully introduced for stage IV GC. Yoshida et al divided stage IV GC into four subcategories: potentially resectable metastasis; marginally resectable metastasis; incurable and unresectable, except for certain circumstances of local palliation needs; and noncurable metastasis.[38] Staging laparoscopy is required in most categories, followed by open procedures. There are no large-scale RCTs dealing with minimally invasive conversion surgery. A retrospective study comparing open surgery and MIS in conversion surgery has been reported recently. Yamamoto et al reported that MIS could be safely performed as conversion surgery following chemotherapy for stage IV GC over open surgery in terms of less blood loss (10 vs 520 mL, $P < .0001$), shorter hospitalization (8 vs 12 d, $P < .0001$), better median relapse-free survival (31.0 vs 11.3 mo, $P = .022$), and median overall survival (52.7 vs 22.4 mo, $P = .0028$) despite the longer operation time.[39] Moreover, MIS was not a negative prognostic factor for overall survival after conversion surgery (HR 0.44, 95% CI: 0.15–1.10; $P = .081$). MIS for conversion surgery could be considered a potential treatment option for stage IV GC. However, due to a lack of evidence, further studies are required to confirm this.

6 | OUR EXPERIENCE

Our institution has experience of over 10 000 cases of gastrectomies for GC, including over 8000 cases of minimally invasive gastrectomies since its foundation. In MIS for EGC, we have been very eager to develop single or reduced port surgery,[40] function-preserving gastrectomy such as pylorus-preserving gastrectomy (PPG) for EGC located at the middle third,[41] proximal gastrectomy (PG) for EGC located at the upper third,[42,43] and limited gastrectomy with sentinel node navigation surgery using dual dye and the isotope method.[44,45] We were a major participant of KLASS-01 comparing LG with OG in clinical stage I GC[5] and KLASS 02 comparing LG with OG in AGC.[17] We have been actively participating in other KLASS-initiated clinical trials.

Before actively adopting MIS for AGC, we conducted a single-center nonrandomized Phase II clinical trial, an AGC trial, to verify the safety and efficacy of LG in AGC.[46,47] The short-term and long-term outcomes of this trial were very convincing for us. We recently analyzed the short-term and long-term outcomes of patients who underwent LG for AGC in our institution.[48] Between May 2003 and December 2018, with a total of 1483 patients, the short- and long-term oncologic outcomes were comparable to those of other studies regarding OG. In detail, 5-y OSR and DFSR were 88.9% and 85.4% in stage IB, 88.7% and 87.2% in stage IIA, 84.2% and 78.1% in stage IIB, 71.7% and 65.6% in stage IIIA, 56.8% and 60.8% in stage IIIB, 45.4% and 25.2% in stage IIIC, and 25.0% for stage IV. The overall recurrence rate was 14.4%, of which peritoneal recurrence was the most frequent (5.2%). The overall 30-d postoperative complication rate was 9.1%, of which pulmonary complication (2.9%) was the most frequent, followed by leakage (2.2%). The old age (OR 1.02, 95% CI: 1.01–1.04, $P = 0.010$) was an independent risk for complications in multivariate analysis. These studies, even retrospective analyses, suggest the potential of LG for AGC to show better short-term results and the same long-term outcomes.

7 | CONCLUSION

In the era of MIS, many open procedures for GC have been reproduced laparoscopically. MIS is associated with fewer complications, favorable short-term outcomes, and a comparable long-term survival rate, even in AGC. MIS implementation for GC has expanded beyond locally resectable AGC to certain selected unresectable GCs and conversion surgery fields.

ACKNOWLEDGEMENTS

None.

DISCLOSURE

The authors declare no conflicts of interest for this article.

ORCID

Hyung-Ho Kim https://orcid.org/0000-0002-8916-0048

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc. 1994;4(2):146–8.
3. Ikeda O, Sakaguchi Y, Aoki Y, et al. Advantages of totally laparoscopic distal gastrectomy over laparoscopically assisted distal gastrectomy for gastric cancer. Surg Endosc. 2009;23(10):2374–9.
4. Chen K, Pan Y, Cai J-Q, Xu X-W, Wu D, Mou Y-P. Totally laparoscopic gastrectomy for gastric cancer: a systematic review and meta-analysis of outcomes compared with open surgery. World J Gastroenterol. 2014;20(42):15867.
5. Kim H-H, Han S-U, Kim M-C, 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. 2019;5(4):506–13.
6. Kim W, Kim H-H, Han S-U, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer. Ann Surg. 2016;263(1):28–35.
7. Katai H, Mizusawa J, Katayama H, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. Lancet Gastroenterol Hepatol. 2020;5(2):142–51.
8. Katai H, Mizusawa J, Katayama H, et al. Short-term surgical outcomes from a phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric cancer: Japan Clinical Oncology Group Study JCOG0912. Gastric Cancer. 2017;20(4):699–708.
9. Liu F, Huang C, Xu Z, et al. Morbidity and mortality of laparoscopic vs. open total gastrectomy for clinical stage I gastric cancer: the CLASS02 multicenter randomized clinical trial. JAMA Oncol. 2020;6(10):1590–7.
10. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018. Gastric Cancer. 2021;24(1):1–21.
11. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer. 2019;19(1):1–48.
12. Katai H, Mizusawa J, Katayama H, et al. Single-arm confirmatory trial of laparoscopy-assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG1401. Gastric Cancer. 2019;22(5):999–1008.
13. Jung DH, Ahn SH, Park DJ, Kim HH. Proximal gastrectomy for gastric cancer. J Gastric Cancer. 2015;15(2):77.
14. Kim H-H, Han S-U, Kim M-C, 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. 2014;32(7):627–33.
15. Yu J, Huang C, Sun Y, et al. Effect of laparoscopic vs. open distal gastrectomy on 3-y disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. JAMA. 2019;321(20):1983–92.
16. Hu Y, Huang C, Sun Y, et al. Morbidity and mortality of laparoscopic versus open D2 distal gastrectomy for advanced gastric cancer: a randomized controlled trial. J Clin Oncol. 2016;34(12):1350–7.
17. Hyung WJ, Yang H-K, Park Y-K, et al. Long-term outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer: The KLASS-02-RCT randomized clinical trial. J Clin Oncol. 2020;38(28):3304–13.
18. Lee H-J, Hyung WJ, Yang H-K, 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. 2019;270(6):983–91.
19. Oba K, Paoletti X, Alberts S, et al. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. J Natl Cancer Inst. 2013;105(21):1600–7.
20. 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. 2015;39(11):2734–41.
21. Zou Z-H, Zhao L-Y, Mou T-Y, et al. Laparoscopic vs. open D2 gastrectomy for locally advanced gastric cancer: a meta-analysis. World J Gastroenterol. 2014;20(44):16750.
22. Chen X, Feng X, Wang M, Yao X. Laparoscopic versus open distal gastrectomy for advanced gastric cancer: A meta-analysis of randomized controlled trials and high-quality non-randomized comparative studies. Eur J Surg Oncol. 2020;46(11):1998–2010.
23. Quan Y, Huang A, Ye M, et al. Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis. Gastric Cancer. 2016;19(3):939–50.
24. Du J, Zheng J, Li Y, et al. Laparoscopy-assisted total gastrectomy with extended lymph node resection for advanced gastric cancer - reports of 82 cases. Hepatogastroenterology. 2010;57(104):1589–94.
25. Lee J-H, Ahn S-H, Park DJ, et al. Laparoscopic total gastrectomy with D2 lymphadenectomy for advanced gastric cancer. World J Surg. 2012;36(10):2394–9.
26. Lee SR, Kim HO, Son BH, et al. Laparoscopic-assisted total gastrectomy versus open total gastrectomy for upper and middle gastric cancer in short-term and long-term outcomes. Surg Laparosc Endosc Percutan Tech. 2014;24(3):277–82.
27. Oh Y, Kim MS, Lee YT, et al. Laparoscopic total gastrectomy as a valid procedure to treat gastric cancer option both in early and advanced stage: a systematic review and meta-analysis. Eur J Surg Oncol. 2020;46(1):33–43.
28. Kodera Y, Yoshida K, Kumamaru H, et al. Introducing laparoscopic total gastrectomy for gastric cancer in general practice: a retrospective cohort study based on a nationwide registry database in Japan. Gastric Cancer. 2019;22(1):202–13.
29. Huscher CG, Mingoli A, Sgarzini G, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-y results of a randomized prospective trial. Ann Surg. 2005;241(2):232–7. doi:10.1097/01.sla.0000151892.35922.f2

30. van der Veen A, Brenkman HJ, Seesing MF, et al. Laparoscopic versus open gastrectomy for gastric cancer (LOGICA): a multicenter randomized clinical trial. J Clin Oncol. 2021;39(9):978–89.
31. Bracale U, Merola G, Pignata G, et al. Laparoscopic gastrectomy for stage II and III advanced gastric cancer: long-term follow-up data from a Western multicenter retrospective study. Surg Endosc. 2021. doi:10.1007/s00464-021-08505-y. Online ahead of print.
32. Uyama I, Suda K, Nakauchi M, et al. Clinical advantages of robotic gastrectomy for clinical stage I/II gastric cancer: a multi-institutional prospective single-arm study. Gastric Cancer. 2019;22(2):377–85.
33. Guerrini GP, Esposito G, Magistri P, et al. Robotic versus laparoscopic gastrectomy for gastric cancer: The largest meta-analysis. Int J Surg. 2020;82:210–28.
34. Fujitani K, Yang H-K, Mizusawa J, et al. gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309–18.
35. Min S-H, Won Y, Lee K, et al. Laparoscopic gastrectomy and metastasectomy for stage IV gastric cancer. Surg Endosc. 2021;35(4):1879–87.
36. Navarra G, Musolino C, Venneri A, et al. Techniques OI. Palliative antecolic isoperistaltic gastrojejunostomy: a randomized controlled trial comparing open and laparoscopic approaches. Surg Endosc. 2006;20(12):1831–4.
37. Ojima T, Nakamori M, Nakamura M, et al. Laparoscopic gastrojejunostomy for patients with unresectable gastric cancer with gastric outlet obstruction. J Gastrointest Surg. 2017;21(8):1220–5.
38. Yoshida K, Yamaguchi K, Okumura N, et al. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer. 2016;19(2):329–38.
39. Yamamoto K, Omori T, Hara H, et al. Minimally invasive surgery is feasible after preoperative chemotherapy for stage IV gastric cancer. Ann Gastroenterol Surg. 2020;4(4):396–404.
40. Ahn SH, Son SY, Jung DH, Park DJ, Kim HH. Pure single-port laparoscopic distal gastrectomy for early gastric cancer: comparative study with multi-port laparoscopic distal gastrectomy. J Am Coll Surg. 2014;219(5):933–43. doi:10.1016/j.jamcollsurg.2014.07.009
41. Suh YS, Han DS, Kong SH, et al. Laparoscopy-assisted pylorus-preserving gastrectomy is better than laparoscopy-assisted distal gastrectomy for middle-third early gastric cancer. Ann Surg. 2014;259(3):485–93. doi:10.1097/SLA.0b013e318294d142
42. Ahn SH, Lee JH, Park DJ, Kim HH. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. Gastric Cancer. 2013;16(3):282–9. doi:10.1007/s10120-012-0178-x
43. Ahn SH, Jung DH, Son SY, Lee CM, Park DJ, Kim HH. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. Gastric Cancer. 2014;17(3):562–70. doi:10.1007/s10120-013-0303-5. Epub 2013 Sep 20 PMID: 24052482
44. Park DJ, Kim HH, Park YS, et al. Simultaneous indocyanine green and (99m)Tc-antimony sulfur colloid-guided laparoscopic sentinel basin dissection for gastric cancer. Ann Surg Oncol. 2011;18(1):160–5. doi:10.1245/s10434-010-1221-y
45. Park DJ, Park YS, Son SY, et al. Long-term oncologic outcomes of laparoscopic sentinel node navigation surgery in early gastric cancer: a single-center, single-arm, phase II trial. Ann Surg Oncol. 2018;25(8):2357–65. doi:10.1245/s10434-018-6523-5
46. Lee JH, Son SY, Lee CM, Ahn SH, Park DJ, Kim HH. Morbidity and mortality after laparoscopic gastrectomy for advanced gastric cancer: results of a phase II clinical trial. Surg Endosc. 2013;27(8):2877–85. doi:10.1007/s00464-013-2848-0. Epub 2013 Feb 13 PMID: 23404155
47. Ahn SH, Kang SH, Lee Y, et al. Long-term survival outcomes of laparoscopic gastrectomy for advanced gastric cancer: five-y results of a phase II prospective clinical trial. J Gastric Cancer. 2019;19(1):102–10. doi:10.5230/jgc.2019.19.e6. Epub 2019 Mar 12. PMID: 30944763; PMCID: PMC6441772
48. Min S-H, Won Y, Kim G, et al. 15-y experience of laparoscopic gastrectomy in advanced gastric cancer: analysis on short-term and long-term oncologic outcome. Surg Endosc. 2020;34(11):4983–90.

How to cite this article: Lee SJ, Kim H-H. Minimally invasive surgery in advanced gastric cancer. Ann Gastroenterol Surg. 2022;6:336–343. doi:10.1002/ags3.12559