How Much Progress Has Been Made in Minimally Invasive Surgery for Gastric Cancer in Korea?: A Viewpoint From Korean Prospective Clinical Trials

Ki-Han Kim, MD, PhD, Sung-Heun Kim, MD, PhD, and Min-Chan Kim, MD, PhD

Abstract: Gastric cancer is the most common cancer in Korea. Because the incidence of gastric cancer is still high even with early detection and because of developments in surgical instruments and technological advances, minimally invasive surgery has rapidly become an accepted treatment for gastric cancer in Korea. Many Korean gastric surgeons have contributed to the rapid adaptation of minimally invasive surgery for gastric cancer: not only the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group, but also other expert surgeons after the 2000s. Thanks to their vigorous efforts involving active learning, education, workshops, academic communications, and international communications with active laparoscopic gastric surgeons in Korea, numerous results and well-designed large-scale clinical studies have been published or are actively ongoing, thus increasing its wide acceptance as an option for gastric cancer. Now, Korea has become one of the leading countries using minimally invasive surgery for the treatment of gastric cancer. This review article will summarize the current status and issues, as well as the clinical trials that have finished or are ongoing, regarding minimally invasive surgery for gastric cancer in Korea.

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INTRODUCTION

Gastric cancer is one of the most common digestive cancers worldwide, and it is the fourth most common cancer and the second leading cause of cancer-related death, with about 700,000 deaths annually. The incidence of early gastric cancer (EGC) in Korea has been increasing because of recent improvements in early diagnosis. As the EGC proportion and age of gastric cancer patients have increased, many surgeons are increasingly interested in minimally invasive surgery (MIS) as represented by laparoscopic gastrectomy. MIS for gastric cancer has gained popularity because it provides better short-term and long-term results. Laparoscopic gastrectomy is most actively performed for the treatment of gastric cancer. Laparoscopically assisted gastrectomy for distal EGC has already gained acceptance because it is minimally invasive and is a suitable alternative to open surgery. Moreover, surgeons experienced in minimally invasive gastrectomy techniques have suggested that these techniques could be successfully applied to the treatment of advanced gastric cancer (AGC). Today, because of surgical instrument innovations and technological advances, several treatments for gastric cancer are now shifting to a new era. These new MIS techniques for gastric cancer include endoscopic resection, various laparoscopic gastric reconstruction methods, robotic surgery, single-port surgery, sentinel lymph node navigation surgery (SNNS), etc. The aim of this article was to review the clinical trials that have finished or are ongoing regarding MIS for gastric cancer in Korea.

Laparoscopic Gastrectomy in EGC and AGC

The purpose of laparoscopic surgery for gastric cancer is to minimize surgical damage and to maximize patients’ quality of life, while not influencing radical operation. In the case of EGC, the role of MIS was obvious and widely accepted. The results of several randomized controlled trials have revealed the feasibility and safety of MIS for EGC. In Korea, a retrospective multicenter trial had been conducted between open distal gastrectomy (ODG) and laparoscopic distal gastrectomy (LDG) in Stage I gastric cancer from April 1998 to December 2005 by the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group. From a prospectively collected gastric cancer database of a multicenter hospital, 3053 patients were enrolled in this study. Many reports were published to compare open gastrectomy with laparoscopic gastrectomy based on a KLASS retrospective database. Recently, the long-term results from the KLASS retrospective trial were published. In this case–control study, the overall survival, disease-specific survival, and recurrence-free survival (median follow-up...
Clinical trial that compared laparoscopic and open D2 gastrectomies for locally advanced gastric cancer (KLASS-02-RCT, NCT01456598). Currently, KLASS-02-RCT is ongoing.

Laparoscopic total gastrectomy (LTG) remains challenging as a laparoscopic approach, and the technique has not been standardized. There were a number of small series advocating LTG for gastric cancer that have appeared in literature. However, because of its technical difficulties and concerns regarding serious complications, LTG has not yet become popularized as LADG has. Moreover, there have been few reports comparing the short-term and long-term outcomes of LTG with conventional open total gastrectomy (COTG) for gastric cancer. Recently, Haverkamp et al reported a meta-analysis on LTG that compared COTG for patients with gastric cancer. According to their meta-analysis, LTG demonstrated less perioperative blood loss, less postoperative complications, and shorter hospital stays, as compared with COTG, although the operative time was longer for LTG. The KLAS group also published a KLAS retrospective study on postoperative outcomes that involved 131 patients who underwent LTG. Jeong et al showed that the rate of postoperative morbidity rate 19% (25/131 patients) but had no mortalities. They concluded that LTG is a safe and feasible procedure for gastric cancer patients. However, a multicenter randomized controlled trial or prospective study on LTG for gastric cancer should be required. Therefore, in Korea, the KLAS group started a phase II, multicenter, single-arm trial evaluating the feasibility of laparoscopic-assisted total gastrectomy (LATG) for stage I gastric cancer (KLASS-03, NCT01584336). In this study, 20 surgeons from 17 institutions participated and performed LTGS on 170 patients. The enrollment of patients who had LTG has already finished. We are awaiting the results regarding the feasibility of LATG.

**Laparoscopic Function-Preserving Gastrectomy**

As for the development of laparoscopic techniques and instruments, MIS has been considered in function-preserving surgery for gastric cancer. Among the various function-preserving surgeries for gastric cancer, representative surgeries include pylorus-preserving gastrectomy (PPG) and proximal gastrectomy (PG). Initially, PPG was the surgical option for gastric cancer that provided a better quality of life and oncologic safety if used for selected types of gastric cancer. Advantages of PPG include pylorus-preserving gastrectomy (LAPPG) showed that LAPPG has the advantages of PPG. However, LAPPG has not been widely performed in Korea. In the 2009 Korean national survey, PPG was only performed for 86 cases (0.6%). Because of the potential of lymph node metastases at the suprapyloric and infrapyloric areas, oncologic safety should be considered if the indication for this method is strictly limited to the middle third of EGC that is located more than 4 cm from the pylorus. Moreover, a laparoscopic approach for PPG is difficult for inexperienced surgeons because it should preserve the vagus nerve and vessels around the pylorus area. However, other reports on laparoscopic-assisted pylorus-preserving gastrectomy (LAPPG) showed that LAPPG is safe for oncological procedures with minimal complications and has the advantages of PPG. Suh et al indicated that the overall postoperative morbidity rate was similar between LADG and LAPPG. Delayed gastric emptying was less frequent in LADG than in LAPPG (1.7% vs 7.8%, respectively; \( P = 0.015 \)). However, all the other complications rates were significantly higher with LADG than in LAPPG (17.0% vs
be a useful gastrectomy option for gastric cancer patients. Moreover, decreases in serum protein and albumin 1 to 6 months postoperatively, as well as decreases in abdominal fat 1 year postoperatively, were significantly greater with LADG than in LAPPG. They concluded that LAPPG could be considered as a better treatment option than LADG in terms of nutrition. Nonetheless, it is necessary to consider LAPPG and to conduct multicenter, prospective, randomized trials in Korea.

A PG for gastric cancer was a rare operation in Korea. Because of complications such as anastomotic strictures and reflux esophagitis that were markedly higher in the PG group and substantially affected quality of life, most gastric surgeons are concerned about performing PGs. Nevertheless, there were several reports of laparoscopy-assisted proximal gastrectomy (LAPG) and robotic gastrectomy. Ahn et al indicated that LAPG is a feasible and acceptable method for treating proximal EGC in terms of surgical and oncologic safety. However, the incidence of reflux symptoms was significantly higher in the LAPG group (32.0 vs 3.7%, respectively; \( P < 0.001 \)). Thus, anti-reflux procedures should be considered to prevent reflux symptoms after LAPG. In this respect, problems still exist, including reducing anti-reflux symptoms and difficulty performing the operative techniques. Recently, experienced surgeons investigated and reported on various types of reconstruction methods and the technical feasibility of these methods after LAPG.

Currently, the KLAS group is studying LAPPG and LATG in multicenter, prospective trials. The KLAS group named and started the KLAS-04 study of evaluating LAPPG, as compared with LDG. Moreover, the LAPG study, called KLAS-05, has also begun.

In the near future, if the number of gastric cancer patients who are candidates for function-preserving surgeries such as LAPPG or LAPG continues to increase, LAPP or LAPG may be a useful gastrectomy option for gastric cancer patients.

Laparoscopic Sentinel Lymph Node Navigation Surgery

Sentinel nodes (SNs) are defined as the first lymph node that receives lymphatic drainage from the primary cancer; therefore, cancer metastasis should occur first in sentinel nodes. Thus, in cancers that do metastasize to lymph nodes, such as breast cancer, melanoma, and gastric cancer, sentinel node detection may be useful in the determination of the extent of lymph node dissection. This concept is known as sentinel lymph node navigation surgery (SNNS). However, the role of SNNS for gastric cancer remains to be elucidated, even though numerous investigations have been performed to increase the sensitivity of sentinel lymph node (SN) detection. SNNS for breast cancer and melanomas has been accepted worldwide and established as a reasonable oncologic surgery. However, SNNS is still in its infancy in the field of gastric cancer. To use SNNS in clinical practice for gastric cancer, first, skip metastases and false negative rate are crucial points. In gastrointestinal malignancies, the appearance of lymph node metastasis is not constant mainly because of the existence of multiple complex lymphatic routes. Thus, in gastric cancer, sentinel lymph nodes can be detected in unpredictable locations. There is a report in which skip metastases occurred in 20% to 30% of gastric cancer. Second, it is still unclear which dye and radioisotope are better than another. The accuracy of SN detection was approximately 90%. There were several review articles and meta-analyses that already reported on sentinel lymph nodes in gastric cancer. For standardization, many surgeons have accumulated their experiences regarding SNNS and discussed SNNS techniques. Because of the limitations of dyes or radioisotopes as a single tracer, other methods were developed. Recently, dual-tracer methods, in which dye and radioisotope tracers are used together, seem to be more effective than any single tracer. Dual-tracer methods are currently considered the most reliable method for the detection of sentinel lymph nodes in patients with EGC.

Recent advances in SNNS and minimally invasive interventions have significantly impacted our current approach for gastric cancer surgery. Appropriate indications for partial (wedge) resection, segmental gastrectomy (PGG), and EGC for cT1NO gastric cancer could be individually determined based on sentinel lymph node status. Various types of laparoscopic function-preserving surgeries are applicable to cancer patients who are negative for metastases in their sentinel lymph nodes during intraoperative pathological diagnosis. For example, laparoscopic partial (wedge) resection of the stomach is applicable for patients with a sentinel lymphatic basin on the greater curvature side.

Furthermore, a combination of laparoscopic SN biopsy and endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) for EGC is another attractive option as a novel, whole stomach-preserving, minimally invasive approach. If all sentinel lymph nodes are pathologically negative for cancer metastases, theoretically, instead of gastrectomy, EMR/ESD may be sufficient for the curative resection of cT1 gastric cancer beyond EMR criteria.

In Korea, the study group named SENORITA (SENtinel Node OREnted Tailored Approach, phase III trial) was launched and included surgeons, gastroenterologists, pathologists, and nuclear medicine doctors. For this phase III study, a quality control study was completed and is undergoing data analysis (NCT01544413). The quality control measures were checked using the performance of 7 critical steps for and SN biopsy comprising the endoscopic, surgical, and pathological procedures. If the SN biopsies were performed perfectly for 10 patients after the completion of the 7 steps, then that institution could participate in the phase III trials. This phase III study trial is now ongoing and will help clarify SNNS for gastric cancer (NCT01804998).

Robotic Gastrectomy in Korea

Robotic gastrectomy has been introduced for gastric cancer treatment as an improved technology to help overcome the technical limitations of laparoscopy. Robotic gastrectomy may have some benefits such as 3-dimensional imaging, surgical instrument with a high degree of angulation, filtration of resting tremor, and an ergonomically comfortable position for surgeons. Robotic surgery was applied to gastric cancer in Korea earlier than in any other country. Although there were some disadvantages such as the lack of tactile sense, similar number of trocars, longer operation time, higher cost, and the lack of articulation of ultrasonic shears, several reports indicated the comparable short-term postoperative outcomes and oncologic outcomes, as compared with laparoscopic gastrectomy. To investigate the role of robotic gastrectomy for gastric cancer, evidence regarding the surgical feasibility of robotic gastrectomy with a large number of patients is necessary to compare with laparoscopic gastrectomy. In Korea, the KLAS group started to conduct a multicenter prospective, case-matched,
clinical trial comparing robotic versus laparoscopic gastrectomy for EGC (NCT01309256). Initially, the study group retrospectively analyzed all robotic gastrectomies that were performed in Korea. After the registration of the retrospective robotic group, a prospective study had been started comparing robotic and laparoscopic groups. Enrollment included 1650 cases. This clinical trial completed enrollment in 2012. This study will investigate surgical complications, quality of life, immunologic response, and cost-effectiveness. The results of this study will contribute evidence regarding clinical indications and efficacy of gastric cancer treatment.

**Single-Incision or Reduced Port Laparoscopic Gastrectomy**

With development of techniques and laparoscopic surgical instruments, several advanced gastrectomy techniques for gastric cancer have made MIS possible. Typical examples of advanced gastrectomy techniques for gastric cancer are single-incision or reduced port laparoscopic gastrectomy. Single-port surgery was first performed in 1969 with gynecological procedures such as tubal ligation. Since then, the use of single-port laparoscopic surgery has widely increased in surgical fields such as cholecystectomy, appendectomy, colectomy, and morbid obesity surgery. There was the first report on successful single-incision laparoscopic gastrectomy for EGC.

Recently, some experienced surgeons who have performed a large number of laparoscopic gastrectomy procedures have also performed using 5 trocars in the umbilicus and abdomen. First, in the early period of single-incision or reduced port laparoscopic gastrectomy have been performed. First, in the early period of 1990s, a small group of young surgeons interested in MIS discussed adequate laparoscopic techniques and better laparoscopic instruments. Increasing interest in MIS for gastric cancer occurred after 2000, so many surgeons actively participated in symposiums or animal labs for its application in gastric cancer (KLASS group was started and activated in 2003). Now, MIS has rapidly become an accepted treatment for gastric cancer as a treatment option for EGC in the early 1990s. In the late 1990s, a small group of young surgeons interested in MIS such as laparoscopy-assisted gastrectomy for EGC discussed adequate laparoscopic techniques and better laparoscopic instruments. Increasing interest in MIS for gastric cancer occurred after 2000, so many surgeons actively participated in symposiums or animal labs for its application in gastric cancer (KLASS group was started and activated in 2003). Now, MIS has rapidly become an accepted treatment for gastric cancer in Korea. Because the incidence of gastric cancer is still high and the number of large-volume centers with experienced surgeons has increased, numerous well-designed studies have been continued or finished. We think that the KLASS group might contribute as a leading group, which could be performed with many RCTs. Recently, the KLASS group was introduced as research highlights.

**Various Anastomotic Techniques After Laparoscopic Gastrectomy for Gastric Cancer**

In the prior era of open gastrectomy, operative techniques mainly performed included gastroduodenostomy (Billroth-I), gastrojejunostomy (Billroth-II), and Roux-en-Y anastomosis. As MIS has become a widely accepted treatment for gastric cancer, various anastomotic techniques for laparoscopic gastrectomy have been performed. First, in the early period of laparoscopic gastrectomy, extracorporeal anastomosis was mainly performed for subtotal and total gastrectomy anastomoses. However, many experienced surgeons are switching from an extracorporeal anastomosis to an intracorporeal anastomosis to obtain more cosmetic benefits and to reduce pain from a mini-laparotomy wound to improve patients’ quality of life. Totally laparoscopy-assisted gastrectomy is a representative procedure. Many experienced surgeons demonstrated their technique and its feasibility and safety in Korea. Second, as for increasing intracorporeal anastomosis techniques, various anastomotic methods have been introduced including gastro-duodenostomy, gastrojejunostomy, and esophageojejunostomy with or without a Roux-en-Y reconstruction. In the case of gastroduodenostomy, techniques using a linear stapler, such as a delta-shape anastomosis, were mostly performed. Gastro-jejunostomy is now easily performed using only a linear stapler during an intracorporeal anastomosis. Moreover, gastrojejunostomy with a Roux-en-Y anastomosis was frequently performed to prevent bile reflux in the remnant stomach and postoperative complications. Recently, as similar procedure, uncut Roux-en-Y gastrojejunostomy has been performed by some experienced surgeons.

In the case of LTG, there are many esophageojejunostomy methods that could accomplish an anastomosis with feasibility and safety. Recently, several investigators introduced technical tips or instruments for esophageojejunostomy, such as the transorally inserted anvil method, side-to-side anastomosis using a linear stapler, intracorporeal circular-stapled esophageojejunostomy using hand-sewn purse-string sutures, and the hemi-double stapling technique. In the KLASS-03 trials (NCT01584336), they will evaluate the difference in surgical outcomes (duration of anastomosis, failure rate of anastomosis, etc.) and postoperative morbidity (anastomotic leakage, stenosis, bleeding, etc.) according to the reconstruction methods after gastrectomy. Additionally, although various techniques or a new technique for MIS in gastric cancer was performed and agreed upon by many experienced surgeons, a well-designed prospective clinical trial is necessary.

In Korea, only a few surgeons performed MIS for gastric cancer as a treatment option for EGC in the early 1990s. In the late 1990s, a small group of young surgeons interested in MIS such as laparoscopy-assisted gastrectomy for EGC discussed adequate laparoscopic techniques and better laparoscopic instruments. Increasing interest in MIS for gastric cancer occurred after 2000, so many surgeons actively participated in symposiums or animal labs for its application in gastric cancer (KLASS group was started and activated in 2003). Now, MIS has rapidly become an accepted treatment for gastric cancer in Korea. Because the incidence of gastric cancer is still high and the number of large-volume centers with experienced surgeons has increased, numerous well-designed studies have been continued or finished. We think that the KLASS group might contribute as a leading group, which could be performed with many RCTs. Recently, the KLASS group was introduced as research highlights.
important issue. Therefore, more large-scale clinical trials are necessitated for the wide application of MIS to gastric cancer.

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