OPEN

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.

(*Medicine* 93(28):e233)

Abbreviations: AGC = advanced gastric cancer, COTG = conventional open total gastrectomy, EGC = early gastric cancer, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, KLASS = Korean Laparoscopic Gastrointestinal Surgery Study, LADG = laparoscopic-assisted distal gastrectomy, LAPG = laparoscopy-assisted proximal gastrectomy, LAPPG = laparoscopic-assisted pylorus-preserving gastrectomy, LATG = laparoscopy-assisted total gastrectomy, LTG = laparoscopic total gastrectomy, MIS = minimally invasive surgery, NCTNumber = ClinicalTrials.gov Identifier, ODG = open distal gastrectomy, PG = proximal gastrectomy, PPG = pylorus-preserving gastrectomy, RCT = randomized controlled trial, SENORITA = SEntinel Node ORIented Tailored Approach, SIDG = single-incision laparoscopic distal gastrectomy, SN = Sentinel node, SNNS = sentinel lymph navigation surgery, TLDG = totally laparoscopic distal gastrectomy.

Editor: Franck Billmann.
Received: August 5, 2014; revised: October 1, 2014; accepted: October 2, 2014.
From the Department of Surgery, Dong-A University College of Medicine, Busan, Korea.
Correspondence: Min Chan Kim, Department of Surgery, Dong-A University College of Medicine, 3-1 Dongdaeshin-Dong, Seo-Gu, Busan 602-715, Korea (e-mail: mckim@donga.ac.kr).
Funding source: This work was supported by the Dong-A University research fund.
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000233

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.[1] The incidence of early gastric cancer (EGC) in Korea has been increasing because of recent improvements in early diagnosis.[2] 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. Laparoscopy-assisted gastrectomy for distal EGC has already gained acceptance because it is minimally invasive and is a suitable alternative to open surgery.[3] 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).[4–7] 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 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.[3,8,9] 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.[10] 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.[11–17] Recently, the long-term results from the KLASS retrospective trial were published.[10] In this case–control study, the overall survival, disease-specific survival, and recurrence-free survival (median follow-up

period, 70.8 months) were not statistically different at each cancer stage, with the exception of an increased overall survival rate for patients with stage IA cancer treated with laparoscopy (laparoscopic group, 95.3%; open group, 90.3%; $P < 0.001$). After using a propensity scoring system for matching, the overall survival, disease-specific survival, and recurrence-free survival rates were not statistically different at each stage. The morbidity and mortality of the case-matched group also had no statistical significance ($P = 0.184$; $P = 1.000$). This study serves as a springboard for phase III multicenter, randomized controlled trials for EGC. The KLASS-01 trial, which was the first multicenter, large-scale, prospective, randomized controlled trial for EGC, was quickly enrolling. During the KLASS-01 trial, an interim analysis was reported in 2010.[18] This interim analysis included 179 laparoscopic-assisted distal gastrectomy (LADG) and 163 ODG patients, and there was no significant difference between LADG and ODG patients in terms of age, gender, comorbidity, postoperative complication rates, morbidity, or mortality. Then, the KLASS-01 trial completed enrollment in 2010. The primary endpoint of KLASS-01 is overall survival, and the secondary endpoints are disease-free survival, morbidity, mortality, quality of life, inflammatory and immune responses, and cost-effectiveness. Fifteen surgeons from 12 institutions recruited 1415 patients. Now, we await the long-term results of the KLASS-01 trial (NCT00452751).[19]

Open surgery has been the standard of care for AGC. Although no evidence or guidelines exist to indicate the use of MIS for AGC, several experienced surgeons have recently attempted to extend the application of laparoscopy-assisted gastrectomy for the treatment of AGC.[4–7,20] Although laparoscopic gastrectomy with D2 lymph node dissection is being performed for patients with locally advanced gastric cancer, the completeness of a D2 lymph node dissection during laparoscopic surgery has not been evaluated, and no standardized procedure exists. Therefore, a multicenter, prospective, randomized trial is necessary regarding laparoscopic gastrectomy for AGC. In Korea, a multicenter, prospective, randomized study regarding LADG for AGC (KLASS-02) had been discussed.[21] The aim of this multicenter, prospective randomized trial was to ensure the non-inferiority of laparoscopic gastrectomy, as compared with open surgery for locally advanced gastric cancer. Moreover, the primary endpoint of KLASS-02 was the 3-year disease-free survival rate of gastrectomy with D2 lymph node dissection for locally advanced gastric cancer. However, no system existed to evaluate the quality of D2 lymph node dissection during a gastrectomy procedure for AGC. Furthermore, no study had been conducted to standardize D2 lymphadenectomy during a laparoscopic or open gastrectomy. Therefore, the KLASS-02 trial group conducted a quality control study to form a consensus regarding D2 lymphadenectomy and to help qualify surgeons who could perform both laparoscopic and open D2 gastrectomies for locally advanced gastric cancer (KLASS-02-QC, NCT01283893).[21] In this quality control study that is currently ongoing, all surgeons will have to submit 3 laparoscopic and 3 open D2 gastrectomy videos. Each video will be assigned to 5 peer reviewers; thus, each surgeon's operations will have a total of 30 reviews. Based on the experts' blinded assessment of the unedited videos, a separate review evaluation committee will decide whether the evaluated surgeon will participate in KLASS-02-RCT. Through this quality control study, 19 surgeons have been already enrolled in the next KLASS-02-RCT study. This quality control trial will be a successful implementation of a subsequent clinical trial that compared laparoscopic and open D2 lymphadenectomies 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.[22–24] 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[25] reported a meta-analysis on LTG that compared COTG for patients with gastric cancer. According to their meta-analysis, LTG demonstrated less intraoperative blood loss, less postoperative complications, and shorter hospital stays, as compared with COTG, although the operative time was longer for LTG. The KLASS group also published a KLASS retrospective study on postoperative outcomes that involved 131 patients who underwent LTG.[14] Jeong et al[14] 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 KLASS group started a phase II, multicenter, single-arm trial evaluating the feasibility of laparoscopy-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 LATG 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 less dumping syndrome, less bile reflux, less weight loss, and decreased gallstone formation.[26,27] However, PPG has not been widely performed in Korea. In the 2009 Korean national survey, PPG was only performed for 86 cases (0.6%).[28] Because of the potential of lymph node metastases at the suprapyloric and infrapyloric areas, oncologic safety should to 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.[29,30] 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.[31,32] Suh et al[31] 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

7.8%, respectively; $P = 0.023$). 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.[33–35] Nevertheless, there were several reports of laparoscopy-assisted proximal gastrectomy (LAPG).[36,37] Ahn et al[37] 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.[38,39] In Korea, there was a prospective, randomized controlled trial regarding LAPG and LATG for upper gastric cancer (NCT01433861).

Currently, the KLASS group is studying LAPPG and LAPG in multicenter, prospective trials. The KLASS group named and started the KLASS-04 study of evaluating LAPPG, as compared with LDG. Moreover, the LAPG study, called KLASS-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, LAPPG 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.[40] 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 node (SN) detection.[41] 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.[42] Second, it is still unclear which dye and radioisotope are better than another.[43] The accuracy of SN detection was approximately 90%.[44,45] There were several review articles and meta-analyses that already reported on sentinel lymph nodes in gastric cancer.[46–48] 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.[49–51] 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, PPG, and PG for cT1N0 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.[52,53]

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.[54]

In Korea, the study group named SENORITA (SEntinel Node ORIented 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.[55–57] 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 KLASS 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.[58] Since then, the use of single-port laparoscopic surgery has widely increased in surgical fields such as cholecystectomy, appendectomy, colectomy, and morbid obesity surgery.[59] There was the first report on successful single-incision laparoscopic gastrectomy for EGC.[60] Recently, more reports with a small number of ECG patients from a single institution were published.[61,62] They showed that single-incision laparoscopic gastrectomy was a feasible and safe procedure for EGC and provides a good cosmetic result. In Korea, there was a prospective, randomized controlled study between pure single-incision laparoscopic distal gastrectomy (SIDG) and totally laparoscopic distal gastrectomy (TLDG) for EGC (NCT01938326). Although this study is a single institutional study, we expect positive results regarding SIDG.

Generally, laparoscopic gastrectomy for gastric cancer was performed using 5 trocars in the umbilicus and abdomen. Recently, some experienced surgeons who have performed a large number of laparoscopic gastrectomy procedures have also performed reduced port laparoscopic gastrectomy for gastric cancer. There were some reports regarding the feasibility and safety of this reduced port laparoscopic gastrectomy technique.[63,64]

In the case of single-incision or reduced port laparoscopic gastrectomy for gastric cancer, there has been no prospective, randomized clinical trial as of yet. Thus, these techniques necessitate more discussion and introduction by experienced surgeons for other laparoscopic gastric surgeons to accept. Additionally, any real benefits should be demonstrated in patients with gastric cancer, not just a cosmetic advantage.

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.[65–69] Second, as for increasing intracorporeal anastomosis techniques, various anastomotic methods have been introduced including gastroduodenostomy, gastrojejunostomy, and esophagojejunostomy 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.[66,70] Gastrojejunostomy 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.[71] Recently, as similar procedure, uncut Roux-en-Y gastrojejunostomy has been performed by some experienced surgeons.[62,72,73]

In the case of LTG, there are many esophagojejunostomy methods that could accomplish an anastomosis with feasibility and safety. Recently, several investigators introduced technical tips or instruments for esophagojejunostomy, such as the transorally inserted anvil method,[74] side-to-side anastomosis using a linear stapler,[75] intracorporeal circular-stapled esophagojejunostomy using hand-sewn purse-string sutures,[76] and the hemi-double stapling technique.[77] 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.[78]

CONCLUSIONS

During the past 15 years, MIS for the treatment of gastric cancer has become a standard procedure in Korea. In gastric cancer, any expert surgeons have contributed to the feasibility and safety of MIS, as well as the oncologic evidence for MIS. Thanks to their contribution through active learning, education, workshops, academic communications, and international communications, well-designed large-scale clinical studies were completed or are actively ongoing in Korea. Moreover, young surgeons who will start performing MIS for gastric cancer might be early adaptors of MIS. However, patient safety is always an

important issue. Therefore, more large-scale clinical trials are necessitated for the wide application of MIS to gastric cancer.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Hyung WJ, Kim SS, Choi WH, et al. Changes in treatment outcomes of gastric cancer surgery over 45 years at a single institution. *Yonsei Med J.* 2008;49:409–415.
3. Kitano S, Shiraishi N, Fujii K, et al. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. *Surgery.* 2002;131:S306–S311.
4. Uyama I, Suda K, Satoh S. Laparoscopic surgery for advanced gastric cancer: current status and future perspectives. *J Gastric Cancer.* 2013;13:19–25.
5. Hur H, Jeon HM, Kim W. Laparoscopy-assisted distal gastrectomy with D2 lymphadenectomy for T2b advanced gastric cancers: three years' experience. *J Surg Oncol.* 2008;98:515–519.
6. Yoshimura F, Inaba K, Kawamura Y, et al. Clinical outcome and clinicopathological characteristics of recurrence after laparoscopic gastrectomy for advanced gastric cancer. *Digestion.* 2011;83: 184–190.
7. Chun HT, Kim KH, Kim MC, Jung GJ. Comparative study of laparoscopy-assisted versus open subtotal gastrectomy for pT2 gastric cancer. *Yonsei Med J.* 2012;53:952–959.
8. Lee JH, Han HS, Lee JH. A prospective randomized study comparing open vs laparoscopy-assisted distal gastrectomy in early gastric cancer: early results. *Surg Endosc.* 2005;19:168–173.
9. 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.* 2008;248:721–727.
10. 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.* 2014;32:627–633.
11. Kim W, Song KY, Lee HJ, et al. The impact of comorbidity on surgical outcomes in laparoscopy-assisted distal gastrectomy: a retrospective analysis of multicenter results. *Ann Surg.* 2008;248:793–799.
12. Kim MC, Kim W, Kim HH, et al. Risk factors associated with complication following laparoscopy-assisted gastrectomy for gastric cancer: a large-scale korean multicenter study. *Ann Surg Oncol.* 2008;15:2692–2700.
13. Song KY, Hyung WJ, Kim HH, et al. Is gastrectomy mandatory for all residual or recurrent gastric cancer following endoscopic resection? A large-scale Korean multi-center study. *J Surg Oncol.* 2008;98:6–10.
14. Jeong GA, Cho GS, Kim HH, et al. Laparoscopy-assisted total gastrectomy for gastric cancer: a multicenter retrospective analysis. *Surgery.* 2009;146:469–474.
15. Cho GS, Kim W, Kim HH, et al. Multicentre study of the safety of laparoscopic subtotal gastrectomy for gastric cancer in the elderly. *Br J Surg.* 2009;96:1437–1442.
16. Lee HJ, Kim HH, Kim MC, et al. The impact of a high body mass index on laparoscopy assisted gastrectomy for gastric cancer. *Surg Endosc.* 2009;23:2473–2479.
17. Song J, Lee HJ, Cho GS, et al. Recurrence following laparoscopy-assisted gastrectomy for gastric cancer: a multicenter retrospective analysis of 1,417 patients. *Ann Surg Oncol.* 2010;17:1777–1786.
18. Kim HH, Hyung WJ, Cho GS, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report: a phase III multicenter, prospective, randomized Trial (KLASS Trial). *Ann Surg.* 2010;251:417–420.
19. Kim HH, Han SU, Kim MC, et al. Prospective randomized controlled trial (phase III) to comparing laparoscopic distal gastrectomy with open distal gastrectomy for gastric adenocarcinoma (KLASS 01). *J Korean Surg Soc.* 2013;84:123–130.
20. Gordon AC, Kojima K, Inokuchi M, et al. Long-term comparison of laparoscopy-assisted distal gastrectomy and open distal gastrectomy in advanced gastric cancer. *Surg Endosc.* 2013;27:462–470.
21. 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.* 2014;14:209.
22. Uyama I, Sugioka A, Fujita J, et al. Laparoscopic total gastrectomy with distal pancreatosplenectomy and D2 lymphadenectomy for advanced gastric cancer. *Gastric Cancer.* 1999;2:230–234.
23. Usui S, Yoshida T, Ito K, et al. Laparoscopy-assisted total gastrectomy for early gastric cancer: comparison with conventional open total gastrectomy. *Surg Laparosc Endosc Percutan Tech.* 2005;15:309–314.
24. Topal B, Leys E, Ectors N, et al. Determinants of complications and adequacy of surgical resection in laparoscopic versus open total gastrectomy for adenocarcinoma. *Surg Endosc.* 2008;22:980–984.
25. Haverkamp L, Weijs TJ, van der Sluis PC, et al. Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis. *Surg Endosc.* 2013;27:1509–1520.
26. Nunobe S, Sasako M, Saka M, et al. Symptom evaluation of long-term postoperative outcomes after pylorus-preserving gastrectomy for early gastric cancer. *Gastric Cancer.* 2007;10:167–172.
27. Park Do J, Lee HJ, Jung HC, et al. Clinical outcome of pylorus-preserving gastrectomy in gastric cancer in comparison with conventional distal gastrectomy with Billroth I anastomosis. *World J Surg.* 2008;32:1029–1036.
28. Jeong O, Park YK. Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. *J Gastric Cancer.* 2011;11:69–77.
29. Takeuchi H, Kitagawa Y. Is pylorus-preserving gastrectomy universally applicable to early gastric cancer of the mid stomach? *Ann Surg Oncol.* 2014;21:356–357.
30. Morita S, Katai H, Saka M, et al. Outcome of pylorus-preserving gastrectomy for early gastric cancer. *Br J Surg.* 2008;95:1131–1135.
31. 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;259:485–493.
32. Jiang X, Hiki N, Nunobe S, et al. Postoperative outcomes and complications after laparoscopy-assisted pylorus-preserving gastrectomy for early gastric cancer. *Ann Surg.* 2011;253:928–933.
33. Katsoulis IE, Robotis JF, Kouraklis G, Yannopoulos PA. What is the difference between proximal and total gastrectomy regarding postoperative bile reflux into the oesophagus? *Dig Surg.* 2006;23: 325–330.
34. An JY, Youn HG, Choi MG, et al. The difficult choice between total and proximal gastrectomy in proximal early gastric cancer. *Am J Surg.* 2008;196:587–591.
35. Kim JH, Park SS, Kim J, et al. Surgical outcomes for gastric cancer in the upper third of the stomach. *World J Surg.* 2006;30:1870–1876.
36. Matsui H, Okamoto Y, Nabeshima K, et al. Endoscopy-assisted gastric resection: a safe and reliable procedure for tumor clearance during laparoscopic high distal or proximal gastrectomy. *Surg Endosc.* 2009;23:1146–1149.

37. Ahn SH, Lee JH, Park Do J, 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: 282–289.

38. Kinoshita T, Gotohda N, Kato Y, et al. Laparoscopic proximal gastrectomy with jejunal interposition for gastric cancer in the proximal third of the stomach: a retrospective comparison with open surgery. *Surg Endosc.* 2013;27:146–153.

39. Ahn SH, Jung DH, Son SY, et al. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. *Gastric Cancer.* 2014;17:562–570.

40. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392–399.

41. Miyashiro I. What is the problem in clinical application of sentinel node concept to gastric cancer surgery? *J Gastric Cancer.* 2012;12:7–12.

42. Kosaka T, Ueshige N, Sugaya J, et al. Lymphatic routes of the stomach demonstrated by gastric carcinomas with solitary lymph node metastasis. *Surg Today.* 1999;29:695–700.

43. Uenosono Y, Natsugoe S, Higashi H, et al. Evaluation of colloid size for sentinel nodes detection using radioisotope in early gastric cancer. *Cancer Lett.* 2003;200:19–24.

44. Lee JH, Ryu KW, Kim CG, et al. Sentinel node biopsy using dye and isotope double tracers in early gastric cancer. *Ann Surg Oncol.* 2006;13:1168–1174.

45. Kim MC, Kim HH, Jung GJ, et al. Lymphatic mapping and sentinel node biopsy using 99mTc tin colloid in gastric cancer. *Ann Surg.* 2004;239:383–387.

46. Ryu KW, Eom BW, Nam BH, et al. Is the sentinel node biopsy clinically applicable for limited lymphadenectomy and modified gastric resection in gastric cancer? A meta-analysis of feasibility studies. *J Surg Oncol.* 2011;104:578–584.

47. Lips DJ, Schutte HW, van der Linden RL, et al. Sentinel lymph node biopsy to direct treatment in gastric cancer. A systematic review of the literature. *Eur J Surg Oncol.* 2011;37:655–661.

48. Wang Z, Dong ZY, Chen JQ, Liu JL. Diagnostic value of sentinel lymph node biopsy in gastric cancer: a meta-analysis. *Ann Surg Oncol.* 2012;19:1541–1550.

49. 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: 160–165.

50. Lee JH, Park Do J, Kim YH, et al. Clinical implementations of preoperative computed tomography lymphography in gastric cancer: a comparison with dual tracer methods in sentinel node navigation surgery. *Ann Surg Oncol.* 2013;20:2296–2303.

51. Kitagawa Y, Takeuchi H, Takagi Y, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. *J Clin Oncol.* 2013;31:3704–3710.

52. Takeuchi H, Saikawa Y, Kitagawa Y. Laparoscopic sentinel node navigation surgery for early gastric cancer. *Asian J Endosc Surg.* 2009;2:13–17.

53. Takeuchi H, Oyama T, Kamiya S, et al. Laparoscopy-assisted proximal gastrectomy with sentinel node mapping for early gastric cancer. *World J Surg.* 2011;35:2463–2471.

54. Bok GH, Kim YJ, Jin SY, et al. Endoscopic submucosal dissection with sentinel node navigation surgery for early gastric cancer. *Endoscopy.* 2012;44:953–956.

55. Song J, Oh SJ, Kang WH, et al. Robot-assisted gastrectomy with lymph node dissection for gastric cancer: lessons learned from an initial 100 consecutive procedures. *Ann Surg.* 2009;249:927–932.

56. Park JY, Kim YW, Ryu KW, et al. Emerging role of robot-assisted gastrectomy: analysis of consecutive 200 cases. *J Gastric Cancer.* 2013;13:255–262.

57. Hyun MH, Lee CH, Kwon YJ, et al. Robot versus laparoscopic gastrectomy for cancer by an experienced surgeon: comparisons of surgery, complications, and surgical stress. *Ann Surg Oncol.* 2013;20:1258–1265.

58. Wheeless CR. A rapid, inexpensive, and effective method of surgical sterilization by laparoscopy. *J Reprod Med.* 1969;3:65–69.

59. Ahmed I, Paraskeva P. A clinical review of single-incision laparoscopic surgery. *Surgeon.* 2011;9:341–351.

60. Omori T, Oyama T, Akamatsu H, et al. Transumbilical single-incision laparoscopic distal gastrectomy for early gastric cancer. *Surg Endosc.* 2011;25:2400–2404.

61. Kong J, Wu SD, Su Y. Translumenal single-incision laparoscopy radical gastrectomy with D2 lymph node dissection for early gastric cancer—primary experience with less invasive surgery in China. *J Laparoendosc Adv Surg Tech A.* 2013;23:141–145.

62. Ahn SH, Son SY, Lee CM, et al. Intracorporeal uncut Roux-en-Y gastrojejunostomy reconstruction in pure single-incision laparoscopic distal gastrectomy for early gastric cancer: unaided stapling closure. *J Am Coll Surg.* 2014;218:e17–e21.

63. Kunisaki C, Ono HA, Oshima T, et al. Relevance of reduced-port laparoscopic distal gastrectomy for gastric cancer: a pilot study. *Dig Surg.* 2012;29:261–268.

64. Kawamura H, Tanioka T, Shibuya K, et al. Comparison of the invasiveness between reduced-port laparoscopy-assisted distal gastrectomy and conventional laparoscopy-assisted distal gastrectomy. *Int Surg.* 2013;98:247–253.

65. Song KY, Park CH, Kang HC, et al. Is totally laparoscopic gastrectomy less invasive than laparoscopy-assisted gastrectomy?: prospective, multicenter study. *J Gastrointest Surg.* 2008;12: 1015–1021.

66. Kim MG, Kawada H, Kim BS, et al. A totally laparoscopic distal gastrectomy with gastroduodenostomy (TLDG) for improvement of the early surgical outcomes in high BMI patients. *Surg Endosc.* 2011;25:1076–1082.

67. Lee J, Kim D, Kim W. Comparison of laparoscopy-assisted and totally laparoscopic Billroth-II distal gastrectomy for gastric cancer. *J Korean Surg Soc.* 2012;82:135–142.

68. Kim HS, Kim MG, Kim BS, et al. Comparison of totally laparoscopic total gastrectomy and laparoscopic-assisted total gastrectomy methods for the surgical treatment of early gastric cancer near the gastroesophageal junction. *J Laparoendosc Adv Surg Tech A.* 2013;23:204–210.

69. Kim HS, Kim BS, Lee S, et al. Reconstruction of esophagojejunostomies using endoscopic linear staplers in totally laparoscopic total gastrectomy: report of 139 cases in a large-volume center. *Surg Laparosc Endosc Percutan Tech.* 2013;23:e209–e216.

70. Kanaya S, Kawamura Y, Kawada H, et al. The delta-shaped anastomosis in laparoscopic distal gastrectomy: analysis of the initial 100 consecutive procedures of intracorporeal gastroduodenostomy. *Gastric Cancer.* 2011;14:365–371.

71. Kojima K, Yamada H, Inokuchi M, et al. A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy. *Ann Surg.* 2008;247:962–967.

72. Uyama I, Sakurai Y, Komori Y, et al. Laparoscopy-assisted uncut Roux-en-Y operation after distal gastrectomy for gastric cancer. *Gastric Cancer.* 2005;8:253–257.

73. Yun SC, Choi HJ, Park JY, Kim YJ. Total laparoscopic uncut Roux-en-Y gastrojejunostomy after distal gastrectomy. *Am Surg.* 2014;80:E51–E53.

74. Jeong O, Park YK. Intracorporeal circular stapling esophagojejunostomy using the transorally inserted anvil (OrVil) after laparoscopic total gastrectomy. *Surg Endosc.* 2009;23:2624–2630.

75. Inaba K, Satoh S, Ishida Y, et al. Overlap method: novel intracorporeal esophagojejunostomy after laparoscopic total gastrectomy. *J Am Coll Surg.* 2010;211:e25–e29.

76. Kinoshita T, Oshiro T, Ito K, et al. Intracorporeal circular-stapled esophagojejunostomy using hand-sewn purse-string suture after laparoscopic total gastrectomy. *Surg Endosc.* 2010;24:2908–2912.

77. Omori T, Oyama T, Mizutani S, et al. A simple and safe technique for esophagojejunostomy using the hemidouble stapling technique in laparoscopy-assisted total gastrectomy. *Am J Surg.* 2009;197:e13–e17.

78. Villanueva MT. Gastric cancer: a master KLASS in laparoscopic gastrectomy. *Nat Rev Clin Oncol.* 2014;11:119.