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KLASS (Korean Laparoendoscopic Gastrointestinal Surgery Study Group) trials: a 20-year great journey in advancing surgical clinical research for gastric cancer

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The Korean Laparoendoscopic Gastrointestinal Surgery Study Group (KLASS) trial series represents a comprehensive body of surgical clinical trials and studies focused on laparoscopic techniques in the treatment of gastric cancer. These trials, conducted and overseen by the KLASS, began with KLASS 01 in 2006 and have progressed to their 14th series as of December 2024. To date, approximately 36 papers, including pivotal publications, have been featured in high-impact journals, significantly advancing the field of gastric cancer treatment. Their findings have been incorporated into gastric cancer treatment guidelines in Korea, Japan, and China, underscoring their influence and clinical relevance. I take immense pride in being part of this remarkable journey, alongside esteemed seniors, colleagues, and numerous clinical researchers who initiated KLASS in 2004. This paper aims to review the studies conducted within the KLASS series to date and provide insights insight into the ongoing the ongoing research initiatives being developed by this esteemed group on their behalf.

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Key Words: Clinical trial, Gastrectomy, Gastric cancer, Laparoscopic surgery

INTRODUCTION

The trends of Korean surgical clinical medicine in the late 1990s and early 2000s, when the Korean Gastric Cancer Study Group was founded in 1993 and the Korean Gastric Cancer Association (KGCA) was founded in 1996, can be summarized in two significant developments.

First, the introduction of minimally invasive surgery (MIS) techniques, which expanded explosively throughout the surgical arena after the clinical implementation of laparoscopic cholecystectomy. Surgery for gastric cancer was no exception since the introduction of the first laparoscopic-assisted gastrectomy for gastric cancer in 1991 [1]. Subsequently, most open gastric cancer surgeries were adapted and reproduced using MIS techniques [2].

Second, the emergence of evidence-based medicine underscored the importance of clinical practice guidelines founded on robust evidence rather than those based solely on clinical experience [3]. Conducting clinical trials became essential in establishing evidence-based guidelines. However, at the time, there were a limited number of clinical trials in laparoscopic gastrointestinal surgery. While a few phase 3 trials were conducted, many lacked proper statistical design and rigorous randomization, which hindered the production of

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statistically significant and clinically impactful outcomes [4,5].

This growing need for education, surgical standardization, and high-quality clinical research led to the establishment of KLASS in 2004. In 2005, KLASS held its inaugural general meeting and first regular academic conference, during which the group's mission, vision, and core values were defined. At its core, KLASS prioritized performing world-class clinical research in the field of laparoscopic gastrointestinal surgery [6].

This year marks the 20th anniversary of KLASS. Over the past 2 decades, the group has successfully completed 5 phase 3 studies and 1 prospective cohort study. Currently, KLASS is conducting four phase 3 studies, one phase 2 trial, and three retrospective studies. Through this review article, we aim to objectively assess the significance and achievements of the KLASS series and provide insights into its potential trajectory over the next 20 years.

OVERVIEW OF THE KLASS TRIALS

KLASS 01 trial: Oncologic outcomes of laparoscopic distal gastrectomy *vs*. open distal gastrectomy in cStage I

Background: Laparoscopic gastrectomy is widely performed for early distal gastric cancer due to its reported benefits, including fewer short-term complications and improved quality of life compared to open gastrectomy. However, prior to the KLASS 01 trial, no well-designed phase 3 clinical trial had been conducted to provide sufficient evidence for its long-term oncological safety [4]. To address this gap, a multicenter prospective phase 3 clinical trial was initiated to evaluate the oncological safety of laparoscopic distal gastrectomy.

Purpose: The trial aimed to test the hypothesis that laparoscopic distal gastrectomy provides a non-inferior long-term survival rate compared to open gastrectomy in patients with clinical stage I distal gastric cancer.

Research progress and results: Although the KLASS 01 trial is commonly regarded as a single phase 3 study, it uniquely encompasses elements of phases 1, 2, and 3. In surgical clinical trials, particularly in surgery, defining phases 1 and 2 can be ambiguous compared to pharmaceutical trials in internal medicine [7]. Therefore, we investigated our idea which analyzed the result of laparoscopic gastrectomy for gastric cancer retrospectively as phase I.

- Phase 1: The group retrospectively analyzed data from 2,976 gastric cancer surgeries (1,477 laparoscopic gastrectomies and 1,499 open gastrectomies) to evaluate complications and long-term survival rates across all clinical stages. This analysis confirmed no significant difference in long-term survival rates between laparoscopic and open surgeries, establishing the oncological safety of laparoscopic gastrectomy [8].
- Phase 2: As part of a prospective phase 2 study, surgical safety was assessed by comparing complications in 342 patients who were prospectively randomized. The sample size was determined based on an estimated 17% complication rate for open surgery. This analysis demonstrated comparable surgical safety between the 2 approaches [9].
- Phase 3: The randomized prospective phase 3 study included 1,416 patients (705 laparoscopic distal gastrectomies and 711 open distal gastrectomies). The primary endpoint, 5-year overall survival, was 94.2% for laparoscopic surgery and 93.3% for open surgery, confirming the non-inferiority of laparoscopic surgery (log-rank P = 0.64; difference, 0.9 percentage points; 1-sided 97.5% confidence interval [CI], −1.6 to infinity) [10]. The 5-year cancer-specific survival rates were also similar: 97.1% for laparoscopic surgery and 97.2% for open surgery (log-rank P = 0.91; difference, −0.03 percentage points; 1-sided 97.5% CI, −1.8 to infinity). Secondary outcomes revealed that laparoscopic surgery resulted in fewer wound complications [11].

Achievement: The KLASS 01 trial, which began in January 2006, involved 19 gastric cancer researchers from 17 hospitals in South Korea. Patient recruitment was completed in 2010, with a retrospective cohort of 3,284 patients and a prospective cohort of 1,416 patients. Data analysis was finalized and published in 2017.

This trial produced 14 Science Citation Index (SCI)-indexed publications, including papers in prestigious journals such as *JAMA Oncology*, *Journal of Clinical Oncology*, and *Annals of Surgery*. Collectively, the trial analyzed data from approximately 5,000 patients. Its findings were incorporated into gastric cancer treatment guidelines in Korea, Japan, and China [12-14]. Additionally, the KLASS 01 trial was notable for being the first surgical clinical study to publish its research protocol in a professional journal [15]. This practice has since become standard for most KLASS series studies, ensuring transparency and methodological rigor in surgical research.

KLASS 02 trial: Oncologic outcomes of laparoscopic distal gastrectomy compared to open distal gastrectomy in advanced gastric cancer

Background: Retrospective studies have suggested that laparoscopic distal gastrectomy for advanced gastric cancer achieves survival rates comparable to those of open gastrectomy, extending its potential beyond early gastric cancer [8,16]. Given the significant real-world demand for laparoscopic gastrectomy in advanced gastric cancer and its relevance across numerous countries, the KLASS identified this as a critical area for investigation. This study was therefore undertaken as a key policy initiative of KLASS.

Purpose: This multicenter, prospective, randomized phase 3 clinical trial involved 21 investigators from 13 institutions

and aimed to compare the 3-year relapse-free survival rates of laparoscopic and open gastrectomy for advanced gastric cancer in a cohort of 1,050 patients.

Research progress and results: The trial began enrolling patients in November 2011 and completed recruitment in April 2015. Several key aspects distinguished this study:

- Quality assurance: The quality of surgical procedures performed by each participating surgeon was rigorously assessed using a scientific scoring system. This evaluation involved 29 domestic and 25 international reviewers, ensuring an objective appraisal of surgical quality [17].
- Independent data management: An independent data center was established to secure the statistical objectivity of the study, setting a precedent for subsequent trials.
- Protocol optimization: To enhance study efficiency and objectivity, the trial protocol underwent 5 revisions. These adjustments improved the study's progression and elevated the overall standard of surgical clinical research.

Results: The laparoscopic group demonstrated superior short- and long-term outcomes compared to the open surgery group:

- Early complications: 15.7% in the laparoscopic group *vs.* 23.4% in the open group (P = 0.0027).
- Late complications: 4.7% in the laparoscopic group *vs.* 9.5% in the open group (P = 0.0038), including significantly fewer cases of intestinal obstruction (2.0% *vs.* 4.4%; P = 0.0447, respectively).

In terms of relapse-free survival:

- Three-year relapse-free survival rates were 80.3% (95% CI, 76.0%–85.0%) for the laparoscopic group and 81.3% (95% CI, 77.0%–85.0%) for the open group (log-rank P = 0.726).
- Cox regression analysis (stratified by surgeon): hazard ratio (HR) of 1.035 (95% CI, 0.762–1.406; log-rank P = 0.827; P for non-inferiority = 0.039).
- Cox regression analysis (stratified by pathologic stage): HR of 1.020 (95% CI, 0.751–1.385; log-rank P = 0.900; P for non-inferiority = 0.030).

The study confirmed that laparoscopic distal gastrectomy with D2 lymphadenectomy is comparable to open surgery in terms of relapse-free survival for patients with locally advanced gastric cancer. Based on these findings, laparoscopic distal gastrectomy with D2 lymphadenectomy could be considered a potential standard treatment option for locally advanced gastric cancer [18].

Achievements: This study resulted in the publication of 10 SCI-indexed papers and has been incorporated into gastric cancer treatment guidelines in Korea, Japan, and China [12-14]. Additionally, the trial continues to yield impactful research, with ongoing publications based on its cohort. The findings are frequently cited in the field of gastric cancer surgery research.

Furthermore, the integration of these results with a Chinese phase 3 study cohort is currently underway, which is anticipated to generate a significant global impact in the field of gastric cancer surgery.

KLASS 03 trial: Feasibility of laparoscopic total gastrectomy

Background: Building on the scientific validation achieved for distal gastric cancer through the success of KLASS 01 and 02 trials, KLASS recognized the need for evidence supporting laparoscopic total gastrectomy (LTG). Despite its widespread use in daily clinical practice, LTG requires robust evidence to verify its oncological safety and surgical feasibility, particularly for proximal gastric cancer. Unlike distal cancer, proximal gastric cancer presents unique challenges that necessitate rigorous evaluation of both oncological outcomes and surgical safety. To address this gap, KLASS planned a single-arm prospective phase II clinical trial to rapidly generate evidence regarding the safety of LTG.

Purpose: This trial involved 22 researchers from 19 domestic institutions and leveraged the KLASS's extensive experience with multi-institutional studies acquired during the KLASS 01 and 02 trials. Patient enrollment began in October 2012 and reached the target number within just 16 months. The primary endpoint of the study was to assess surgical complications within 1 month postoperatively, comparing them to the historical complication rate of 18% observed in open total gastrectomy.

Research progress and results: The study demonstrated that the overall complication rate for LTG was 20.6%, while the rate of complications classified as Clavien-Dindo grade III or higher was 9.4%. These rates were not statistically significant compared to the historical control, confirming the safety of LTG [19]. The secondary endpoint examined short-term complications based on the anastomosis method used: extracorporeal circular method, intracorporeal circular stapling method, and intracorporeal linear stapling method.

While no significant differences were observed in the overall complication rates among these techniques, anastomotic stricture occurred more frequently in the intracorporeal circular group [20].

Achievement: This trial was the first prospective study to verify the surgical safety of LTG. It provided valuable insights into various aspects of esophagojejunostomy through prospective observation, contributing significantly to the understanding of surgical techniques for proximal gastric cancer.

Moreover, this study served as a foundational effort, paving the way for the ongoing KLASS 06 trial, a multicenter phase 3 clinical study aimed at evaluating the oncological safety of LTG for advanced gastric cancer. The findings of KLASS 03 continue to play a pivotal role in shaping the future of MIS for proximal gastric cancer.

KLASS 04 trial: Laparoscopic pylorus-preserving gastrectomy *vs*. distal gastrectomy

Background: With the increasing prevalence of early gastric cancer due to the widespread use of upper gastrointestinal endoscopy, there has been growing interest in post-gastrectomy syndrome, particularly dumping syndrome. This has led to a heightened focus on gastric function-preserving surgeries that reduce the extent of gastric resection while preserving the pyloric sinus to maintain physiological function.

Purpose: The KLASS 04 trial was a multicenter, prospective, randomized phase 3 clinical study involving 16 investigators from 9 institutions. The trial enrolled 256 patients (129 laparoscopic pylorus-preserving gastrectomy [LPPG] *vs*. 127 laparoscopic distal gastrectomy) to compare outcomes between standard gastrectomy and gastric function-preserving surgery. The primary endpoint was the incidence of dumping syndrome, defined as a Sigstad score of 7 or higher, occurring within 1 year postoperatively.

Research progress and results: Patient enrollment began in July 2015 and was concluded on schedule in July 2017, with follow-up observations conducted over the subsequent 3 years.

In the short-term results, there was no difference in complication rates between the 2 groups, but delayed gastric emptying occurred significantly higher in the experimental group (LPPG) at 7.2%. In addition, there were no postoperative deaths in either group, and there was no difference in the 3-year survival and recurrence rates between the 2 groups [21]. Among the secondary endpoints, the experimental arm showed an advantage in the occurrence of gallstones, reflux gastritis, postoperative anemia, and hypoproteinemia. In contrast, it showed a disadvantage in delayed gastric emptying and reflux esophagitis. However, there was no difference in the frequency of dumping syndrome, postoperative quality of life, or weight change between the 2 groups [22].

Achievement: The KLASS 04 trial was the first clinical study to directly compare the functional efficacy of laparoscopic surgeries. It set a precedent for future clinical trials evaluating various function-preserving surgical techniques, such as laparoscopic proximal gastrectomy with double-tract reconstruction (LPG-DTR), long-limb Roux-en-Y gastrojejunostomy, and reduced port laparoscopic distal gastrectomy.

Moreover, this was the first study to prioritize functional outcomes as the primary endpoint, contributing significantly to the standardization and broader adoption of gastric function-preserving surgeries that were previously performed in only a limited number of institutions.

This study was also cited in the treatment guidelines of the KGCA, highlighting its influence on clinical practice and its role in advancing surgical innovation [12].

KLASS 05 trial: Laparoscopic proximal gastrectomy with double-tract reconstruction *vs*. laparoscopic total gastrectomy

Background: The incidence of proximal early gastric cancer was rising. However, despite attempts at various esophagogastric anastomosis techniques following proximal gastrectomy, significant complications—such as reflux esophagitis and esophagogastric anastomotic stricture—remained unresolved, leading to the continued preference for total gastrectomy. The introduction of esophagojejunal and gastrojejunal double-tract anastomosis after proximal gastrectomy offered a solution to these complications and renewed interest in proximal gastrectomy as a function-preserving surgical option [23].

Purpose: This multicenter, randomized, phase 3 clinical trial involved 19 investigators from 10 domestic institutions. The study aimed to evaluate the superiority of LPG-DTR as a function-preserving surgery compared to LTG. The primary endpoints were hemoglobin levels and vitamin B12 replacement requirements 2 years postoperatively. A total of 138 patients were enrolled, with 69 randomly assigned to each group.

Research progress and results: The trial was initiated in 2014, with the first patient enrolled in October 2016. Patient recruitment concluded in September 2018, and the final evaluation was completed in September 2020 after a 2-year follow-up period.

Short-term outcomes:

- Complication rates: 23.5% in the LPG-DTR group *vs*. 17.4% in the LTG group (P = 0.373).
- No significant differences in surgical time or blood loss.

Reflux symptoms and Visick scores were similar between groups [24].

Long-term outcomes:

- Hemoglobin levels: Mean changes from baseline to 24 months were –5.6% (standard deviation [SD], 7.4%) in the LPG-DTR group *vs*. –6.9% (SD, 8.3%) in the LTG group, with an estimated difference of –1.3% (95% CI, –4.0% to 1.4%; P = 0.35).
- Vitamin B12 supplementation: The mean cumulative supplementation was 0.4 mg (SD, 1.3) in the LPG-DTR group *vs*. 2.5 mg (SD, 3.0) in the LTG group, with a significant difference of 2.1 mg (95% CI, 1.3–2.9 mg; P < 0.001).
- Late complication rates: 17.6% in the LPG-DTR group *vs*. 10.1% in the LTG group (P = 0.31).
- Reflux esophagitis incidence: Similar between groups (2.9% *vs*. 2.9%, P = 0.99).
- Quality of life: The LPG-DTR group had significantly better physical functioning scores (85.2 [SD, 15.6] *vs*. 79.9 [SD, 19.3], P = 0.03) and social functioning scores (89.5 [SD, 17.9] *vs*. 82.4 [SD, 19.4], P = 0.03) on the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30).

- Survival rates: Two-year overall survival (98.5% in the LPG-DTR group *vs.* 100% in the LTG group, P = 0.33) and disease-free survival (98.5% in the LPG-DTR group *vs.* 97.1% in the LTG group, P = 0.54) were not significantly different between groups [25].

Achievement: This trial was the first to establish the safety and efficacy of proximal gastrectomy as a viable option for proximal early gastric cancer. It played a pivotal role in advancing the development and refinement of various anastomotic techniques for restoring bowel continuity after proximal gastrectomy.

The findings of the KLASS 05 trial have significantly influenced clinical practice and were incorporated into the Korean gastric cancer treatment guidelines [12].

KLASS 06 trial: Laparoscopic total gastrectomy *vs.* open total gastrectomy in advanced gastric cancer

Background: Although the overall incidence of gastric cancer is gradually declining, the incidence of proximal gastric cancer is slowly increasing in Korea. In contrast, proximal gastric cancer constitutes a significant proportion of cases in Western countries [26,27]. Additionally, in regions such as China and Western countries—excluding Korea and Japan—most proximal gastric cancers are diagnosed at advanced stages. This has led to ongoing questions about the oncological safety of laparoscopic surgery for patients in these regions.

Purpose: This study aims to evaluate and compare the oncological safety and treatment outcomes of LTG *vs.* open total gastrectomy in patients with resectable proximal advanced gastric cancer (stages T2–T4a) undergoing radical total gastrectomy with systematic lymphadenectomy (D2 or D2–10).

The primary endpoint is to determine whether LTG is non-inferior to open total gastrectomy in terms of 3-year relapse-free survival. The secondary endpoints include comparisons of surgical complications, mortality rates, recovery times until discharge, 3-year and 5-year overall survival rates, and 5-year relapse-free survival rates between the 2 groups.

Research progress: This is a prospective, 1:1 randomized, phase 3 clinical trial involving 28 investigators from 16 domestic institutions. The study requires a total of 772 patients and follows the KLASS protocol of conducting a participating surgeon qualification study to ensure surgical quality. The trial began in 2018 and successfully completed patient enrollment in October 2024. All enrolled patients are currently under observation, and follow-up data collection is ongoing.

Achievement: The KLASS 06 trial is expected to contribute significantly to the standardization of LTG with D2 dissection techniques and surgical quality management. As there has not yet been a phase 3 clinical study specifically addressing LTG, the results of this trial—regardless of the outcome—are anticipated to have a substantial international impact. Moreover, this trial highlights the KLASS's capacity to conduct large-scale, high-quality clinical research, further cementing its influence in the global surgical community.

KLASS 07 trial: Laparoscopic-assisted distal gastrectomy *vs.* totally laparoscopic distal gastrectomy

Background: Early laparoscopic gastrectomy techniques involved creating a small abdominal incision of approximately 5 cm to retrieve the resected specimen and perform anastomosis. However, advancements in surgical instruments, including automatic staplers, and improvements in surgical techniques through accumulated experience have enabled the transition to a fully laparoscopic approach. In this method, gastric resection and anastomosis are performed entirely within the abdominal cavity, eliminating the need for a mini-laparotomy.

Purpose: This multicenter, prospective, randomized phase 3 clinical trial involved 26 investigators from 21 institutions. The primary endpoint was the comparison of 30-day postoperative morbidity between the experimental group (totally laparoscopic distal gastrectomy [TLDG] without mini-laparotomy) and the control group (laparoscopic-assisted distal gastrectomy [LADG] with mini-laparotomy).

Research progress and results: The study began in March 2018 and completed patient enrollment in August 2021, with a total of 442 patients. Notably, this was the first international collaborative study conducted with China under the KLASS.

- The overall complication rate was lower in the TLDG group (12.2%) compared to the LADG group (17.2%), although the difference was not statistically significant.
- TLDG demonstrated fewer postoperative ileus (0.9% *vs.* 5.7%, P = 0.006) and pulmonary complications (0.5% *vs.* 4.3%, P = 0.035).
- Quality of life assessments showed significant improvements in pain, body image, emotion, and anxiety in the TLDG group, but these differences diminished by 1 year postoperatively [28].

Achievement: KLASS 07 marked the first international joint study conducted in collaboration with China, showcasing the KLASS's expanding influence and ability to collaborate across borders. The trial has resulted in 6 SCI-indexed publications, further contributing to the body of evidence supporting minimally invasive techniques in gastric cancer surgery.

KLASS 08 trial: Laparoscopic *vs.* open distal gastrectomy after neoadjuvant chemotherapy in locally advanced gastric cancer

Background: Recent studies in both Western countries and Korea have demonstrated that surgery following neoadjuvant chemotherapy for resectable locally advanced gastric cancer can improve survival rates [29,30]. As a result, the importance

of perioperative chemotherapy in managing gastric cancer has grown significantly.

Purpose: Neoadjuvant chemotherapy can induce tissue fibrosis or edema, potentially complicating lymphadenectomy during surgery. This trial aims to determine whether laparoscopic gastrectomy, particularly the lymphadenectomy component, can be performed effectively and appropriately after chemotherapy.

Research progress and results: This is a multicenter, prospective phase 2 clinical trial involving 15 institutions. The primary endpoint is to evaluate whether the number of lymph nodes retrieved during laparoscopic gastrectomy is adequate to assess the appropriateness of the surgical procedure.

The study, initiated in 2021, is currently enrolling patients and actively progressing toward its objectives.

Achievement: The KLASS 08 trial is expected to provide critical evidence supporting the expanded indications for laparoscopic surgery in locally advanced gastric cancer. Additionally, it highlights the evolving role of surgeons in multidisciplinary cancer care, particularly in integrating surgery with perioperative chemotherapy. By demonstrating the feasibility and efficacy of laparoscopic gastrectomy in this context, the study aims to strengthen the evidence base for minimally invasive approaches in advanced gastric cancer treatment.

KLASS 09 trial: Long-limb *vs*. conventional bypass reconstruction in type II diabetes

Background: With the increasing westernization of Korean dietary habits, the prevalence of obesity and type 2 diabetes has risen sharply. During this time, the concept of "onco-metabolic surgery" emerged, suggesting that gastric cancer patients with type 2 diabetes who undergo gastrectomy and bypass anastomosis of the duodenum and upper jejunum may experience significant improvement in diabetes [31].

Purpose: This trial is a multicenter, prospective, randomized phase 2 study involving 94 patients. The test group undergoes a long bowel bypass, while the control group receives conventional bypass reconstruction. The primary endpoint is the improvement of diabetes following surgery, measured by transitioning from insulin injections to oral glucose-lowering medications and reducing the dosage of diabetes medications.

Research progress and results: Patient enrollment began in July 2020 and was completed in November 2022, with all 94 patients successfully enrolled. These patients are currently being monitored in follow-up to assess long-term outcomes.

Achievement: As the prevalence of type 2 diabetes continues to rise due to changes in diet and lifestyle, this study has the potential to serve as a critical reference point for surgical approaches targeting gastric cancer patients with metabolic syndrome. The results are expected to provide valuable insights into optimizing surgical strategies for managing type 2 diabetes alongside gastric cancer treatment.

KLASS 10 trial: Partial omentectomy *vs*. total omentectomy in cT3, cT4a gastric cancer

Background: Total omentectomy, traditionally considered a critical component of standard gastrectomy for gastric cancer, has been reported as unnecessary in a phase 3 study conducted in an open surgery setting [32]. Moreover, total omentectomy is time-consuming and particularly challenging during laparoscopic and robotic surgeries, raising questions about its necessity in modern surgical approaches.

Purpose: The primary objective of this trial is to evaluate the oncological outcomes, specifically recurrence and survival rates, based on whether total omentectomy is performed during gastrectomy.

Research progress: This study is designed as a multicenter, prospective, randomized phase 3 clinical trial. Preparations for initiating the trial are currently underway.

Significance: If successful, this study could redefine the standard surgical approach for advanced gastric cancer, potentially reducing surgical complexity and operative time without compromising oncological outcomes.

KLASS 11: Nationwide survey of gastroesophageal junction cancer

Background: The demand for surgery for gastroesophageal junction (GEJ) cancer has increased in recent years, driven by the rising prevalence of esophageal adenocarcinoma and GEJ cancer, particularly in Western countries. In Asian countries such as Korea, Japan, and China, the incidence of GEJ cancer is also gradually increasing, largely due to growing rates of obesity and gastroesophageal reflux disease.

Despite this perceived increase, there has been no comprehensive epidemiological study on GEJ cancer in Korea. A 2019 epidemiological survey conducted by the KGCA confirmed an increase in proximal gastric cancer cases but did not provide detailed insights into cancers of the GEJ [33]. This highlights the urgent need for accurate epidemiological data to better understand the trends and inform clinical management strategies.

Purpose: To address this gap, a large-scale retrospective epidemiological survey is being conducted to analyze the prevalence and characteristics of GEJ cancer in Korea. The study aims to provide a detailed understanding of epidemiological trends and contribute to the development of tailored treatment guidelines.

Research progress: The survey is currently underway, collecting data from across the country to ensure a comprehensive analysis of GEJ cancer cases.

Significance: The findings from this nationwide survey will offer critical insights into the epidemiology of GEJ cancer in Korea, guiding both clinical and policy decisions. It is expected to serve as a foundation for future research and standardize

treatment approaches in the region.

KLASS 12 trial: Reduced port gastrectomy *vs.* conventional distal gastrectomy

Background: Advancements in laparoscopic surgical instruments and the accumulation of surgical expertise have paved the way for minimally invasive techniques that further reduce the number of trocars used during surgery [34]. Reduced port gastrectomy, in theory, offers the benefits of reduced surgical pain for patients and enhanced cosmetic outcomes, aligning with the principles of oncoplastic surgery.

Purpose: The primary endpoint of this study is to compare the rate of postoperative complications within 30 days between reduced port gastrectomy and conventional 5-port gastrectomy.

Research progress: This multicenter, prospective, randomized phase 3 clinical trial involved 21 investigators from 15 institutions. The trial enrolled a total of 348 patients, with a planned enrollment period of 2 years. Despite challenges posed by the COVID-19 pandemic, the first patient was enrolled in June 2022, and enrollment was completed ahead of schedule in October 2023, taking only 16 months.

The data collected is currently being analyzed, and the results are in the process of being submitted for publication.

Significance: The KLASS 12 trial is expected to provide critical evidence on the feasibility and safety of reduced port gastrectomy compared to conventional techniques. By validating its potential to reduce surgical pain and enhance cosmetic outcomes without compromising patient safety, the trial could significantly impact the adoption of reduced port techniques in clinical practice.

KLASS 13 trial: Reduced port robotic gastrectomy

Background and system: Since robotic surgery was introduced into clinical practice, various robotic gastrectomy techniques have been developed and implemented using robotic platforms. Reduced port robotic gastrectomy is 1 such innovation, aiming to minimize invasiveness while leveraging the precision of robotic systems. This study seeks to establish a robotic reduced port gastrectomy registry to standardize surgical techniques, enhance outcomes, and improve patients' quality of life.

Research progress: The trial began in May 2023 as a multicenter, retrospective study. The study aims to enroll between 1,000 and 1,200 cases to build a robust dataset for evaluating and refining reduced port robotic gastrectomy techniques. Patient enrollment and data collection are currently ongoing.

Significance: By establishing a comprehensive registry, this study is expected to provide critical insights into the feasibility, safety, and patient outcomes of reduced port robotic gastrectomy. It will also contribute to the standardization of surgical techniques, helping to optimize robotic surgical practices and improve the quality of life for patients undergoing gastrectomy.

KLASS 14 trial: Hospital cost after minimally invasive surgery

Background: MIS has shown benefits in many aspects. However, its economic features have not been studied in the KLASS series. To understand the economic value of MIS and investigate the factors that may increase hospital costs, herein we conduct a retrospective study.

Purpose: The primary objective of this trial is to evaluate the hospital cost in terms of surgical approach methods.

Research progress: This study is designed as a multicenter, retrospective study. Preparations for initiating the trial are currently underway.

Significance: The findings from this investigation will offer economic insights for surgical treatment in gastric cancer and help understand the true economic value of MIS. It is expected to provide background knowledge on economic feasibility for decision-making.

CONCLUSIONS

The success of the KLASS research series (Table 1) can be attributed to several key factors, which are outlined below.

Shared research leadership

A defining aspect of the KLASS series has been its commitment to shared research leadership. By establishing a transparent and fair research selection system, policy research themes and free research topics are solicited from members annually. Leadership is distributed rather than monopolized, as each study features a different principal investigator, fostering motivation among young researchers. For policy studies, measures such as considering the number of patients registered in previous studies minimized discord during researcher selection.

Rigorous quality control of surgical procedures

The surgical capabilities of participating researchers and the enrollment criteria for patients are critical in surgical research. Unlike most previous studies, which overlooked quality control, KLASS developed a robust surgeon qualification system. Participating researchers were required to meet predefined eligibility criteria, and raw surgical videos were evaluated to ensure competence. This system has been instrumental in maximizing patient safety and improving the validity of research hypotheses.

However, as surgical standardization and quality control have advanced significantly, it may be time to streamline this process with a single qualification assessment to reduce the

Table 1. Summary of KLASS trials

Trial	Title	Phase	No. of patients	Primary endpoint	Status	Result	Achievements
KLASS 01 PI: Hyung-Ho Kim	Prospective randomized controlled trial (phase III) to compare laparoscopic distal gastrectomy with open distal gastrectomy for early gastric cancer	Multicenter, phase I (retrospective), II, III, RCT	Retrospective cohort: 3,284 Prospective cohort: 1,416	5-year overall survival	Finished	No difference in survival	14 SCI papers, including *Journal of Clinical Oncology*, *JAMA Oncology*, *Annals of Surgery* Reflected in the guidelines
KLASS 02 PI: Sang Uk Han	Efficacy of laparoscopic subtotal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer	Multicenter, phase III, RCT	Prospective, 1,050	3-year relapse-free survival	Finished	No difference in survival	10 SCI papers, including *Journal of Clinical Oncology*, *Annals of Surgery*, *JAMA Surgery*, *British Journal of Surgery* Reflected in the guidelines
KLASS 03 PI: Gyu Seok Cho, replaced by Jin-Jo Kim	Prospective multi-center study of laparoscopy-assisted total gastrectomy for clinical stage I gastric cancer	Multicenter, phase II, prospective, observational	Prospective, 168	The incidence of postoperative morbidity and mortality (time frame, 1 month)	Finished	No difference compared to historical results of open total gastrectomy	2 SCI papers
KLASS 04 PI: Hyuk-Joon Lee	Multicenter randomized controlled trial comparing laparoscopic pylorus-preserving gastrectomy (LPPG) versus laparoscopic distal gastrectomy (LDG) for the middle-third early gastric cancer	Multicenter, phase III, prospective, RCT	Prospective, 256	Incidence of dumping syndrome, assessed by Sigstad score (≥7) at 1 year postoperatively	Finished	No difference in dumping syndrome rate Positive results in secondary endpoints	2 SCI papers, including *Annals of Surgery*
KLASS 05 PI: Do Joong Park	Multicenter prospective randomized controlled trial of laparoscopic proximal gastrectomy and laparoscopic total gastrectomy for upper third early gastric cancer	Multicenter, phase III, prospective trial Superiority trial	Prospective, 138	1. Hemoglobin change 2 years after gastrectomy 2. Vitamin B12 cumulative supplement quantity 2 years after gastrectomy	Finished	Superior in vitamin B12 replacement of the experimental arm	2 SCI papers, including *JAMA Open Network* Reflected in the guidelines
KLASS 06 PI: Woo Jin Hyung	Multicenter randomized controlled trial for application of laparoscopic total gastrectomy with lymph node dissection for gastric cancer	Multicenter, prospective, interventional (clinical trial), RCT	Prospective, 772	3-year relapse-free survival	Finished patient's enrollment	Ongoing	
KLASS 07 PI: Sungsoo Park	A multicenter randomized controlled trial comparing the quality of life between laparoscopy-assisted distal gastrectomy and totally laparoscopic distal gastrectomy for gastric cancer	Multicenter, prospective, interventional (clinical trial), RCT	Prospective, 442	Postoperative 30-day morbidity rate	Finished	No difference in complication rate but less pulmonary and postoperative ileus and better QoL of the experimental arm	6 SCI papers First international trial, collaboration with Chinese investigators

Table 1. Continued

Trial	Title	Phase	No. of patients	Primary endpoint	Status	Result	Achievements
KLASS 08 PI: Young Kyu Park	A multicenter prospective phase II comparative study of laparoscopic versus open distal gastrectomy after neoadjuvant chemotherapy for the treatment of locally advanced gastric cancer patients	Multicenter, phase 2, prospective, interventional (clinical trial), RCT	Prospective, 238	Number of harvested lymph nodes in D2 lymph node dissection (time frame: 2 weeks after operation when the pathologic report is available)	Patient's recruitment	Ongoing	
KLASS 09 PI: Jong-Han Kim	Comparison of the effect between long-limb and conventional bypass reconstruction after subtotal gastrectomy in gastric cancer patients with type II diabetes (multicenter prospective randomized controlled study)	Multicenter, phase 2, prospective, interventional (clinical trial), RCT	Prospective, 94	Improvement, transitioning from insulin injection to oral blood glucose drop and reducing the dosage of diabetes drugs (time frame: postoperative)	Finished patient's enrollment	Ongoing	
KLASS 10 PI: In-Gyu Kwon	Multicenter randomized study for comparison between partial omentectomy and total omentectomy during minimally invasive distal gastrectomy and lymphadenectomy in clinical T3 and T4a gastric cancer patients	Multicenter, phase III, prospective, RCT		3-year disease-free survival	Planning	Ongoing	
KLASS 11 PI: Jin-Jo Kim	Nationwide survey of treatment for GEJ cancer	Retrospective cohort study			Ongoing	Ongoing	
KLASS 12 PI: Han Hong Lee	A multicenter randomized controlled trial comparing the safety between reduced port and conventional laparoscopic distal gastrectomy for early gastric cancer	Multicenter, prospective, interventional (clinical trial), RCT	Prospective, 348	Improvement: the incidence of complications 30 days after surgery	Finished	On submission	
KLASS 13 PI: Hyoung-Il Kim	Reduced port robotic gastrectomy (REPROG): development of registry and standardization of surgical process	Multicenter, retrospective data collection	Retrospective, 1,000-1,200		Ongoing	Ongoing	
KLASS 14 PI: Tae-Han Kim	Investigation on economic aspects of MIS gastrectomy for gastric cancer	Multicenter, retrospective data collection		Hospital cost	Planning	Ongoing	

KLASS, Korean Laparoendoscopic Gastrointestinal Surgery Study Group; PI, principal investigator; RCT, randomized controlled trial; SCI, Science Citation Index; QoL, quality of life; GEJ, gastroesophageal junction; MIS, minimally invasive surgery.

burden on participating researchers [35].

RECOMMENDATIONS FOR FUTURE STUDIES

Accelerating research timelines

In the early stages of KLASS, there were no competing research platforms. However, similar research groups have now emerged with comparable interests, making promptness an increasingly critical factor. To maintain leadership, KLASS should work to reduce the time required from study planning to execution, including patient recruitment.

Emphasizing a multidisciplinary approach

The modern standard for gastric cancer research emphasizes multidisciplinary collaboration. Future KLASS studies should explore not only surgical methodologies but also the role of surgical oncology in treating stage 4 gastric cancer. These efforts should position surgeons as key contributors within multidisciplinary teams.

FINAL REFLECTIONS

The KLASS research series represents a landmark effort in evaluating the safety and efficacy of laparoscopic surgery in gastric cancer. These studies have scientifically validated the advantages of laparoscopic surgery and provided critical evidence for clinical treatment guidelines, ultimately shaping modern treatment strategies.

The achievements of the KLASS studies signify meaningful progress in gastric cancer treatment, laying the foundation for improved patient management and better treatment outcomes.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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