

Ongoing surgical clinical trials on minimally invasive surgery for gastric cancer: Korea

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Abstract: Since Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group was activated in 2003, several randomized controlled trials (RCTs) have finished or are ongoing in Korea to evaluate oncologic safety and feasibility of minimally invasive surgery (MIS) for gastric cancer by KLASS group as well as other expert surgeons. MIS in gastric cancer is regarded as one of standard treatment modality for early gastric cancer (EGC) and the indication is going expansion with the accumulation of evidence. This review covers current status of ongoing clinical trials on MIS for gastric cancer in Korea.

Keywords: Gastric cancer; minimally invasive surgery (MIS); clinical trial

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Introduction

Despite the rapid progress in the molecular understanding of gastric cancer and the development of targeted therapies to treat it, currently surgical resection is the only effective treatment option to improve the survival (1-3). Since the first successful gastrectomy for gastric cancer by Theodor Billroth in 1881, the surgical skill has been steadily revising and improving. Remarkable change during recent decades would be the adoption of minimally invasive surgery (MIS) for gastric cancer. Due to the recent improvements in early diagnosis (4), the incidence of early gastric cancer (EGC) in Korea has been increasing and MIS has been rapidly adopted to many Korean gastric cancer surgeons. Moreover, the efforts to build the evidence on feasibility of MIS are being continued. As experience in the use of laparoscopy has accumulated, the inclusion criteria for studies on MIS have been extended to patients with advanced gastric cancer (AGC). Moreover, interests in advanced techniques, such as laparoscopic total gastrectomy (LTG) or extended lymph node dissection has steadily broadened the scope of the studies on MIS. In addition, the effort to find a more suitable surgical treatment option in EGC, such as sentinel node navigation surgery (SNNS) or function

preserving surgery is also continued. The aim of this article is to overview the current status of ongoing clinical trials regarding MIS for gastric cancer in Korea (*Table 1*).

Laparoscopic gastrectomy for EGC

In Korea, the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-01 trials—the first multicenter, large-scale, prospective, randomized controlled trial (RCT) comparing laparoscopic distal gastrectomy (LDG) with open distal gastrectomy (ODG) for EGC—was started in 2006 (NCT00452751). Although several RCTs had been conducted to address the oncologic safety of laparoscopic gastrectomy before commencing KLASS-01, the sample sizes of those studies were not large enough to conclusively demonstrate safety and equivalency compared with open procedures (5-8). The primary end point of the KLASS-01 was 5-year overall survival. The secondary endpoints were disease free survival, morbidity and mortality, quality of life, inflammatory, immune response, and cost-effectiveness. The Enrollment was finished at August 2010; 1,416 patients from 12 centers participated in this study. Recently, the result on morbidity and mortality was reported (9). The overall complication rate was significantly lower in the

Table 1 Prospective multicenter trials of minimal invasive gastrectomy in Korea

Study	KLASS 01	KLASS 02	KLASS 03	KLASS 04	KLASS 05	Robot	SENRORITA
Current status	Enrollment: finished	Enrollment: finished	Enrollment: finished	Recruiting patients	Recruiting participant	Results are reported, data collection for subsequent study	Recruiting patients
Phase	III	III	II	III	III	II (observational matched cohort)	III
Intervention	LDG vs. ODG	LDG vs. ODG	LTG	LAPPG vs. LDG	LPG vs. LTG	RG vs. LG	LSNNS vs. LG
Inclusion criteria	Clinical stage I	cT2-T4a	cT1N0	cT1N0	cT1N0, upper 1/3 location	cT1-T3	cT1N0
Sample size	1,416	1,050	168	256	-	400 (finally 434 were enrolled)	580
Primary endpoint	5-year overall survival	3-year relapse-free survival	Morbidity and mortality	Incidence of Dumping syndrome	-	Morbidity and mortality	3-year disease-free survival
Secondary endpoint	Disease free survival, morbidity and mortality, quality of life, inflammatory and immune response, and cost-effectiveness	3-year overall survival, morbidity and mortality, and postoperative recovery index, and quality of life	The surgical outcomes according to several methods of reconstruction and the postoperative course	3-year relapse-free survival and overall survival, morbidity and mortality, body weight change, fat volume change on abdominal CT scan, change of protein and albumin, quality of life, incidence of gallstone, and gross and microscopic changes measured by gastroscopy	-	Operative time, blood loss, rate of open conversion, recovery of bowel function, length of hospital stay, and financial costs	Morbidity and quality of life
Year started	February 2006	October 2011	October 2012	July 2015	-	May 2011	March 2013
Year of completion (estimated)	August 2015	May 2018	November 2013	June 2023	-	December 2012	December 2022

KLASS, Korean Laparoscopic Gastrointestinal Surgery Study; SENORITA, Sentinel Node Oriented Tailored Approach; LDG, laparoscopic distal gastrectomy; ODG, open distal gastrectomy; LTG, laparoscopic total gastrectomy; LAPPG, laparoscopy-assisted pylorus preserving gastrectomy; LPG, laparoscopic proximal gastrectomy; RG, robot gastrectomy; LG, laparoscopic gastrectomy; LSNNS, laparoscopic sentinel node navigation surgery.

LDG group (13.0%) than in ODG group (19.9%) although there was no difference in interim analysis (10). The difference was mainly due to wound complication (LDG *vs.* ODG; 3.1% *vs.* 7.7%, $P=0.001$). The result confirms the minimally invasiveness of laparoscopic surgery. The final results on oncologic safety are expected to be reported soon.

In spite of rapid progress on surgical skill and instruments, LTG in gastric cancer patients is not widely accepted due to the absence of established optimal methods for anastomosis and the technical difficulty of performing complete D2 lymphadenectomy. To investigate the feasibility of LTG in clinical stage I gastric cancer located in upper 1/3, the KLASS group launched the prospective, multicenter phase II trial (KLASS-03) in 2012. The purposes of this study are to evaluate the incidence of postoperative morbidity and mortality, and to evaluate the surgical outcomes according to several methods of reconstruction. Also, the postoperative course of the patients underwent LTG was analyzed. The enrollment of 168 patients was finished in November 2013. The result of this study will confirm the safety of LTG and propose the optimal method of anastomosis in LTG (NCT01584336).

Laparoscopic gastrectomy for AGC

The standard surgical treatment for AGC is open gastrectomy with D2 lymphadenectomy according to Japanese, NCCN, and ESMO guidelines (11-13). D2 lymphadenectomy is associated with lower loco-regional recurrence and gastric cancer-related death rates compared to gastrectomy with D1 lymphadenectomy (14). However, the actual extent of D2 lymphadenectomy varies among surgeons because of a lacking consensus on the anatomical definition of each lymph node station. It was a big obstacle to perform the RCT comparing laparoscopic and open D2 lymphadenectomy for patients with locally AGC. Therefore, standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC, NCT01283893) were accomplished prior to KLASS-02-RCT trial (15) to build a consensus on D2 lymphadenectomy and to qualify surgeons. Six unedited videos of LDG and ODG were submitted by surgeons for participation and reviewed by international experts using evaluation criteria for completeness of D2 lymphadenectomy. Finally, the review committee made decisions on whether a surgeon's qualification was sufficient to participate in KLASS-02-RCT (16). The primary endpoint of the KLASS-02 RCT is non-inferiority in the 3-year relapse-free survival rate after LDG and D2

lymphadenectomy for locally AGC compared with open conventional surgery. The secondary end-points are 3-year overall survival, morbidity and mortality, postoperative recovery index, and quality of life (NCT0146598). The estimated sample size of KLASS-02 is 1,050. The enrollment of patients was finished in May 2015 and the final results are expected to be reported in 2018. The KLASS-02 trial is the first phase III trial to evaluate the efficacy of LDG with D2 lymphadenectomy for AGC. Also in China (CLASS 01, NCT01609309) and Japan (JLSSG0901, UMIN000003420), a multicenter phase III trials are ongoing to compare LDG and ODG in patients with locally AGC.

Laparoscopic function-preserving surgery

The improved survival rates of cancer patients have increased the interest in patients' post-surgical quality of life. The aim of function preserving surgery in gastric cancer patient is to reduce the functional sequelae of radical gastrectomy such as dumping syndrome, reflux gastroesophagitis and weight loss. Function preserving gastric resections include pylorus-preserving gastrectomy (PPG), proximal gastrectomy (PG), and vagus nerve preserving gastrectomy. With the development of minimally invasive approaches, methods to adopt those function preserving procedures to MIS have been tried.

PPG has been known to have functional advantages in terms of nutritional benefit, lower incidence of dumping syndrome, bile reflux, or gallstone formation, as compared with distal gastrectomy (17-21). However, previous comparative studies between PPG and distal gastrectomy were mostly performed retrospectively by conventional open surgery. In addition, PPG may have potential risks against oncologic safety, including fewer dissected lymph nodes compared to distal gastrectomy (22-24). Although recent large-volume retrospective analyses reported that laparoscopic PPG was oncologically safe and was better than LDG in terms of nutritional advantage and a lower incidence of gallstone formation, prospective RCTs, especially comparing laparoscopic PPG and LDG, are rare (25). To evaluate superiority on postoperative quality of life and comparable survival after laparoscopic PPG compared to LDG in patients with middle-third EGC, KLASS-04 trial is recruiting patients since July 2015 (NCT02595086). The primary endpoint is incidence of dumping syndrome, and secondary endpoints are 3-year relapse-free survival and overall survival, morbidity and mortality, body weight

change, fat volume change on abdominal CT scan, change of protein and albumin, quality of life, incidence of gallstone, and gross and microscopic changes measured by gastroscopy. The estimated sample size is 256. This study will contribute to the wide application of laparoscopic PPG.

Performing PG for gastric cancer has been limited because of anastomosis related complications such as anastomosis stricture and reflux esophagitis, which substantially affected postoperative quality of life after the surgery. Although many investigators reported the various types of reconstructions and feasibility of these methods, there was no RCT comparing laparoscopic PG with LTG (26-28). Recently, double tract reconstruction following PG was reported as feasible and useful method with excellent postoperative outcomes in terms of preventing reflux symptoms (4.65%) and anastomotic stenosis (4.65%) by the investigators in Korea (28). The KLASS group is preparing the KLASS-05 trial comparing Laparoscopic PG with double tract reconstruction and LTG. The primary endpoint is hemoglobin change at post-gastrectomy 2 years, and secondary endpoints are prevalence rate of postoperative reflux esophagitis, anastomotic stricture, incidence of morbidity and mortality, quality of life 2-year after operations and 3-year disease free survivals. The estimated sample size is 180. Currently, recruitment of participating surgeons is in progress.

Sentinel node navigation surgery (SNNS)

SNNS and function preserving surgery share the concept. SNNS, the individualized minimally invasive treatment, may retain the patients' quality of life by preventing various post-gastrectomy syndromes related to unnecessary prophylactic lymph node dissection in patients without lymph node metastasis. However, clinical application of SNNS remains controversial for years because of different study protocol and results between studies (29-34). Main debatable issue for clinical use of SNNS is high false negative rate. However, a recent multicenter trial from Japan showed quite promising results with a low false-negative rate of SN biopsy in early-staged gastric cancer patients (35). In addition, multicenter quality control study (phase II) has been performed recently in Korea prior to phase III trial and tolerable results were observed (0% false negative rate of laparoscopic sentinel node basin dissection) (36). Based on these results, multicenter phase III trial (Sentinel Node Oriented Tailored Approach, SENORITA) to compare the laparoscopic SNNS with laparoscopic gastrectomy for cEGC (cT1N0, less than

3 cm, not indicated to endoscopic submucosal resection) was launched in March 2013 (NCT01804998). The estimated sample size was 580. The primary end-point was 3-year disease-free survival, and the secondary end-points were morbidity and quality of life. Laparoscopic SNNS is expected to assume an important role in gastric cancer treatment through SENORITA trial. However, there are a number of technical problems to be resolved for clinical use of SNNS. These include the accuracy of intraoperative pathological diagnosis, optimal tracer material or method, and the possible applicability of intraoperative endoscopic resection instead of partial gastric resection. Additional studies on SNNS are still required.

Robotic surgery for gastric cancer

Da Vinci robot systems (Intuitive Surgical, Sunnyvale, California, USA) was applied to gastric cancer in Korea since 2005 and several investigators have reported that short-term postoperative outcomes and oncologic outcomes of robot surgery were comparable to laparoscopic gastrectomy (37-40). In addition, meta-analysis results revealed that use of robotic surgery for gastric cancer significantly decreases intraoperative blood loss. Also, comparable morbidity and mortality to laparoscopic surgery was reported (41). However, longer operation time and higher cost are the limitations of clinical application of robotic surgery in gastric cancer in spite of technical superiority over laparoscopic surgery such as 3-dimensional imaging, surgical instrument with a high degree of angulation and filtration of resting tremor. The current indications for robotic surgery are similar to laparoscopic surgery due to a lack of evidence. Therefore, a prospective, multicenter comparative study was conducted in Korea and the short-term outcome was reported recently (NCT01309256). There were no significant differences in morbidity and mortality rates, estimated blood loss, rates of open conversion, diet build-up, and length of hospital stay, but significantly higher cost and longer operation time in robot group were observed as expected (42). Studies on the long-term surgical outcomes are on progress.

Conclusions

This article is a brief outline of ongoing clinical trials on MIS in Korea. Well-designed, large-scale clinical studies had been completed or are actively ongoing. The results of the studies are expected to prove that MIS is as safe

and effective as open conventional surgery. As well as accumulation of evidence, the multicenter prospective studies have contributed to the standardization of the surgical technique. This has also accelerated the subsequent clinical trials. Many unresolved issues of MIS are expected to be addressed in future multicenter prospective studies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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