

Clinical Trial Protocol

Multicenter prospective randomized controlled trial comparing laparoscopic proximal gastrectomy and laparoscopic total gastrectomy for upper third early gastric cancer (KLASS-05)

Version No: V 1.3

Study Summary

Study Title	(English) Multicenter prospective randomized controlled trial of comparing laparoscopic proximal gastrectomy and laparoscopic total gastrectomy for upper third early gastric cancer (KLASS-05)
Principal Investigator	Do Joong PARK, Professor, Department of Surgery, Seoul National University Bundang Hospital
Funding Organization	Medtronic

Study Objectives	To demonstrate the safety, efficacy, and clinical applicability of laparoscopic proximal gastrectomy by comparing postoperative changes in hemoglobin levels and cumulative amount of vitamin B12 supplement (primary endpoints), incidence of reflux esophagitis, quality of life (secondary endpoints), and short-term surgery outcome in patients with upper third early gastric cancer undergoing laparoscopic proximal gastrectomy vs laparoscopic total gastrectomy
Study Design	The study will be conducted at multiple sites, and patients with upper third early gastric cancer will be randomized to receive total gastrectomy or proximal gastrectomy with double tract reconstruction. Clinical outcomes of the two surgical approaches will be compared for two years after surgery.
Study Duration	From the date of IRB approval to 48 months after the approval
Study Population	Patients with proximal gastric cancer (≤ 5 cm in size, cT1N0M0 (7 th UICC TNM)) who meet the inclusion criteria
Number of Subjects	138 (69 for the total gastrectomy arm, 69 for the proximal gastrectomy with double tract reconstruction arm)
Vulnerable Population	Not Applicable
Investigational Drug/Device	Not Applicable
Regimen and Dose	Not Applicable
Study Procedures	1. Patients with proximal gastric cancer (≤ 5 cm, cT1N0M0), as determined by preoperative endoscopy, endoscopic ultrasound, computed tomography, and biopsy results, will be randomly assigned to undergo laparoscopic proximal gastrectomy or laparoscopic total gastrectomy with the patient's consent. 2. Patients randomized to the laparoscopic proximal gastrectomy group will undergo laparoscopic standard radical resection consisting of proximal gastrectomy and lymphadenectomy with double tract reconstruction. Patients randomized to the laparoscopic total gastrectomy group will undergo

	laparoscopic standard radical resection consisting of total gastrectomy and lymphadenectomy with Roux-en-Y reconstruction. 3. Development of anemia is a major concern after laparoscopic total gastrectomy, and changes in hemoglobin level and cumulative total amount of vitamin B12 supplement administered, which are parameters of anemia, will be evaluated as primary endpoints. The incidence of reflux esophagitis, which is known as the most common complication after conventional laparoscopic proximal gastrectomy, will be evaluated as a secondary endpoint using methods such as endoscopy, Visick score, patient questionnaires, changes in nutritional status, and upper gastrointestinal series. Other secondary endpoints will include quality of life, postoperative complications and mortality, and survival (disease-free survival & overall survival). These measures will be compared between the two groups to evaluate the safety, efficacy, and clinical applicability of laparoscopic proximal gastrectomy.
Main Inclusion Criteria	Upper third early gastric cancer, cT1N0M0, lesion $\leq$ 5 cm
Main Exclusion Criteria	Patients with a preoperative diagnosis of anemia, patients in whom total gastrectomy is the only appropriate treatment (presence of other malignant gastric lesions, etc.), and patients with concurrent malignancy that may affect the preserved gastric function.
Efficacy Assessments	Changes in hemoglobin level, total amount of vitamin B12 supplements, quality of life, cost-effectiveness, and oncological outcome will be compared.
Safety Assessments	Early complications within 30 days of surgery, bowel recovery after surgery, time to diet initiation, length of hospital stay, anastomosis-related operation time, anastomosis-related complications and conversion rate to open laparotomy will be reported and evaluated, and an ad hoc investigator meeting will be held for safety assessment by all investigators, if necessary.
Assessment/Visit Schedule	Before surgery and 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months after surgery
Statistical Analysis Methods	T-test, Chi-square test; $p < 0.05$
Anticipated Effects and Expected Results	We expect that this multicenter, prospective, randomized, control trial will demonstrate the advantages of laparoscopic proximal gastrectomy with double tract reconstruction and contribute to expand the indication for laparoscopic proximal gastrectomy in patients with upper third early gastric cancer, ultimately contributing to improved quality of life of patients.

Clinical Trial Protocol

1. Study title

Multicenter prospective randomized controlled trial comparing laparoscopic proximal gastrectomy (LPG) and laparoscopic total gastrectomy (LTG) for upper third early gastric cancer (KLASS-05)

2. Names and addresses of study sites

(Name of study site) Department of Surgery, Seoul National University Bundang Hospital
(Address) 82, Gumi-ro 173beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea 13620

Participating institutions

Seoul National University Hospital
Asan Medical Center
Severance Hospital
Ajou University Hospital
Chonnam National University Hwasun Hospital
The Catholic University of Korea Seoul St. Mary's Hospital
Pusan National University Yangsan Hospital
Gyeongsang National University Jinju Hospital
National Cancer Center

3. Names and titles of principal investigator and co-investigators

Principal Investigator

Do Joong PARK, Professor, Department of Surgery, Seoul National University College of Medicine

4. Sponsor

Not applicable

5. Name and address of the funding organization

(Name of the funding organization) Covidien
(Address) 534, Teheran-ro, Glass Tower BLDG 17th FL, Gangnam-gu, Seoul, Republic of Korea

6. Estimated study duration

From the date of IRB approval to 48 months after approval

7. Study condition

Preoperative clinical stage cT1N0M0 upper third gastric cancer ≤5 cm

8. Background and Objectives

1) Background

(1) Epidemiology and Treatment of Gastric Cancer

Despite extensive research and efforts, cancer remains one of the deadliest diseases that pose a threat to humanity and is the leading cause of death for adults in South Korea. Treatments for gastric cancer include chemotherapy, immunotherapy, radiation therapy, and surgical resection; however, surgical resection is the only potentially curative treatment. In recent years, various chemotherapy regimens have been examined in order to improve long-term survival in gastric cancer. With increasing incidence of early gastric cancer, much research is currently underway in the field of surgery on organ- and function-preserving surgery in order to improve curability as well as the quality of life of patients after surgery.

(2) Proximal Gastric Cancer Treatment

Total gastrectomy has been the conventional approach for both early and advanced proximal gastric cancer that arises in the upper third of the stomach or gastro-esophageal junction. Advantages of total gastrectomy are that it can eliminate the possibility of developing remnant gastric cancer and permits extensive lymph node dissection. However, it leads to substantially decreased quality of life due to high rate of postoperative complications as well as reduced food intake resulting from loss of function and nutritional and metabolic changes caused by malabsorption (2-3). Therefore, there is an increased tendency to preserve the gastric function as much as possible and much research is underway to investigate whether proximal gastrectomy can be adopted as an alternative treatment to total gastrectomy. In proximal gastrectomy, whether the extent of lymph node dissection should include the lymph nodes around the distal stomach (#5, #6) and lymph nodes around the spleen (#10) has always been the subject of debate. In the past, total gastrectomy was performed combined with pancreateosplenectomy due to concerns of metastasis to lymph nodes in these regions. However, it has been demonstrated that survival benefit from this surgical approach is relatively small compared to the high postoperative complications and mortality rate, and currently gastrectomy with spleen or pancreas preservation has become a common procedure (4-6). Factors that determine the splenic lymph node metastasis include tumor location, depth of abdominal wall invasion, and tumor size, and, although overall incidence of lymph node metastasis ranges from 10%-20%, the rate of metastasis is extremely low for early gastric cancer. Therefore, a spleen-preserving surgical approach is commonly used unless an enlarged splenic lymph node or infiltration of the spleen is observed (4,7-9). A recent study analyzing the oncologic characteristics of proximal gastric cancer showed that there is almost no metastasis to lymph nodes around the distal stomach from gastric cancers that are ≤ 5 cm, located close to the lesser curvature, and have noninvasive histological characteristics and depth of invasion confined to the muscular layer (1). The study reported that proximal gastrectomy might be performed instead of total gastrectomy for this type of cancer (1). No differences in short-term and long-term prognosis between the two groups have been reported (10-12). Therefore, it is believed that proximal gastrectomy can be performed instead of total gastrectomy when the tumor has the oncologic characteristics described above.

(3) Changes in reconstruction methods after proximal gastrectomy for gastric cancer

Proximal gastrectomy can be classified by the gastric resection technique and reconstruction method, and reconstruction methods can be further classified by whether a transporter with storage capacity is used or not. Esophago-gastrostomy was commonly performed when proximal gastrectomy was initially introduced. However, postoperative reflux esophagitis and the resulting anastomosis stricture occurred in a significantly high proportion cases, and therefore antireflux procedures, such as fundoplication and valvuloplasty, were performed together or additional procedures, such as balloon dilatation, were required (13-16). Therefore, to overcome these drawbacks of the conventional surgical approach and increase absorptive function or to reduce the incidence of reflux esophagitis, gastric tube reconstruction, techniques using jejunal or colonal, and jejunal pouch interposition, and double track have been used (17-20).

Of these techniques, gastric tube reconstruction was used in 37 laparoscopic cases performed at our institution. Analysis of the results showed that this method has limitations because the incidence of reflux esophagitis was 34.6%, which was not significantly different from that of the conventional reconstruction method. In this study, proximal gastrectomy will be performed with double track reconstruction, which has been recently reported to be associated with reduced incidence of reflux esophagitis compared to the conventional reconstruction method and has shown good results in 15 patients who underwent the procedure at our institution (23).

(4) The pathogenesis of reflux esophagitis after gastrectomy for gastric cancer

Reported incidence of reflux esophagitis following total gastrectomy and proximal gastrectomy performed for gastric cancer treatment varies widely, ranging from 0% to 5% and 7% to 50%, respectively. This wide range appears to be due to slightly different diagnostic criteria for reflux esophagitis used in each study, and various biases inherent in retrospective reports as most of these reports were based on retrospective analysis of data. There are very few prospective studies that have examined the incidence of reflux esophagitis. In the past, reflux esophagitis, a commonly observed complication after gastric cancer surgery, has been known to occur mainly from damage caused by reflux of gastric acid. However, recent studies using the latest diagnostic tools have reported that esophageal mucosal damage from bile or pancreatic juice reflux, rather than from gastric acid reflux, is the major cause of esophageal mucosal damage. However, most results are from studies comparing reconstruction methods after subtotal gastrectomy, and very few studies have investigated reflux esophagitis following total gastrectomy and proximal gastrectomy for proximal gastric cancer treatment. Although the mechanism by which reflux esophagitis occurs is expected to be similar despite different surgical approaches, studying the nature and extent of materials refluxed to the esophagus and incidence of reflux esophagitis after pyloric ring function-preserving surgery may provide useful data for the development of pharmacological treatment of esophagitis and for a surgical approach that may reduce esophagitis. Essentially, reflux esophagitis after gastric surgery can be divided into two types, those caused by acid reflux from the remnant stomach or bile reflux from the duodenum. In order to evaluate the pattern of these two types of reflux, 24 hour pH Holter monitoring (Bravo pH monitoring) of the lower esophagus will be performed before surgery and at 3 months, 6 months, and 12 months after surgery

for evaluation of acid reflux, and 99mTc diisopropyliminodiacetic acid (DISIDA) scan will be performed before surgery and at 3 months, 6 months, and 12 months after surgery for evaluation of bile reflux. For proximal gastrectomy, the actual amount of food passing through the remnant stomach will be assessed by performing upper gastrointestinal series at 12 months after surgery to evaluate the function and volume of the remnant stomach and the degree of reflux depending on the length of the lesser/greater curvatures of the remnant stomach. In addition, changes in reflux characteristics and incidence and mechanism of reflux esophagitis by surgical techniques will be evaluated.

(5) Nutritional status and quality of life of patients after proximal gastric cancer surgery
Patients who undergo total gastrectomy have substantially poorer quality of life after surgery due to reduced food intake, changes in gastrointestinal hormonal environment, and changes in nutritional status as a result of malabsorption. Although proximal gastrectomy is performed as a means to reduce these changes in the patient's quality of life following surgery, very few prospective studies have actually examined differences in long-term nutritional status and quality of life between patients who received proximal gastrectomy and those who received total gastrectomy. Therefore, the present study aims to evaluate the changes in nutritional status by surgical techniques and analyze the association between reflux esophagitis and changes in patient's quality of life using the gastrointestinal quality of life index (GIQLI) and EORTC-c30 and STO22 questionnaires.

(6) Trial importance and rationale

Due to increased opportunity for health examinations in recent years, the detection rate of early gastric cancer and long-term survival after treatment have increased, leading to increased interest in postoperative quality of life. Despite the generalization that laparoscopic surgery has greatly improved the quality of life of patients after surgery, much debate still remains with respect to the effect of the reconstruction method on quality of life, and many studies are underway to determine their relative superiority (21). Different complications may arise and patients have different nutritional status during the recovery process depending on the reconstruction method after upper third gastric cancer surgery, and therefore the reconstruction method is believed to have a significant impact on the quality of life after surgery. Thus, considering curability as well as quality of life of patients with upper third early gastric cancer, studies on appropriate reconstruction methods are needed. Of the many available reconstruction methods, this study will compare conventional esophagojejunostomy after total gastrectomy and double tract reconstruction after proximal gastrectomy in terms of incidence and pathogenesis of reflux esophagitis and nutritional metabolism. We believe this is an important study that can help clinicians decide which treatment method is the most appropriate for patients undergoing surgery for proximal gastric cancer in the future.

2) Hypothesis and objectives

As the proportion of patients with proximal early gastric cancer among gastric cancers diagnosed in South Korea is increasing and given the better pathophysiological understanding of proximal gastric cancer, a large number of studies are being conducted investigating gastric function-preserving surgical approaches (1). However, despite the

use of various reconstruction methods, the incidence of reflux esophagitis remains high, negatively affecting quality of life after gastrectomy and causing many surgeons to abandon proximal gastrectomy. Therefore, the objectives of this study are to compare total gastrectomy, which is still widely performed in proximal gastric cancer, with a surgical proximal gastrectomy technique with double tract reconstruction. The use of this technique has been increasing after it was shown to have good outcomes in a small-scale study (25). Hence, this technique will be used to evaluate the incidence and pathogenesis of reflux esophagitis and postoperative quality of life of patients after LPG, and also to evaluate the efficacy of LPG in proximal early gastric cancer.

9. Code names for investigational drug and device code names (or generic name of active substance), composition, dosage form/formulation (including comparator)

Not applicable.

10. Subject inclusion and exclusion criteria, target sample size and rationale for sample size calculation

1) Inclusion Criteria

- (1) Patients diagnosed with gastric adenocarcinoma by tissue biopsy
- (2) Patients aged 20 to 80 years
- (3) Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- (4) Patients with American Society of Anesthesiology (ASA) score class of I to III
- (5) Patients who voluntarily take part in the present study by signing the written informed consent approved by the institution's IRB prior to study participation after they are given sufficient explanation of the trial's purpose and protocol.
- (6) Patients who can undergo proximal gastrectomy and whose preoperative test results meet the following oncologic characteristics
 - Tumor located in the proximal third of the stomach
 - Tumor $\leq$ 5cm in size
 - Preoperatively staged as $\leq$ cT1 (tumor invasion of the submucosa)/Pre-treatment clinical stage of cT1
 - All lymph nodes not exceeding 8 mm on preoperative tests (especially, lymph nodes #4d, 5, 6, 10)
- (7) Patients who can undergo radical resection/patients who are eligible for curative intent surgical resection

2) Exclusion Criteria

- (1) Patients with a preoperative diagnosis of anemia (Hb 13g/dL for males and Hb 12g/dL for females)
- (2) Patients in whom total gastrectomy is the only appropriate treatment (presence of other malignant gastric lesions in the distal stomach)
- (3) Patients who have undergone chemotherapy or radiotherapy for gastric cancer prior to surgery
- (4) Patients who need combined resection due to other disease (except cholecystectomy)
- (5) Patients with concurrent malignancy that may affect gastric function preservation index

- ① History of malignancy in other organs
- ② Concurrent malignancy in other organs
- (6) Patients with a history of receiving treatment or currently undergoing treatment for systemic inflammatory disease
- (7) Patients with a history of gastrectomy
- (8) Vulnerable subjects (those lacking decision-making capacity, pregnant women, or women planning pregnancy)

3) Target Sample Size and Calculation Rationale

- (1) Primary Endpoint: changes in hemoglobin level and total amount of vitamin B12 supplement at 2 years after surgery
- (2) Retrospective cohort data of Seoul National University Bundang Hospital was used
 - ③ At 2 years after surgery, the rate of reduction of hemoglobin level was $8.6\% \pm 8.5\%$, and total amount of vitamin B12 supplement was $3.1 \text{ mg} \pm 2.2 \text{ mg}$ in patients who underwent LTG
 - ① At 2 years after surgery, the rate of reduction of hemoglobin level was $3.4\% \pm 11.1\%$, and the total amount of vitamin B12 supplement was $0.1 \pm 0.4 \text{ mg}$ in patients who underwent LPG with double tract reconstruction.

(3) Superior test

- ② Null hypothesis: There are no differences between LTG and LPG with double tract reconstruction groups in terms of changes in hemoglobin level and total amount of vitamin B12 supplements.
- ③ Alternative hypothesis: The LPG with double tract reconstruction group is superior to the LTG group in terms of changes in hemoglobin level and total amount of vitamin B12 supplements.

(4) Type I error (alpha): 0.05, Type II error (beta): 0.20

There are two primary efficacy endpoints in this study: total amount of vitamin B12 supplement will be evaluated as a primary efficacy endpoint in addition to the pre-specified primary endpoint of hemoglobin (%). Because there are two primary efficacy endpoints, an alpha-split method will be used to assign an alpha of 4% to hemoglobin (%) and alpha of 1% to total amount of vitamin B12 supplement for multiple comparison test. In other words, p-values less than 4% are considered significant for the hemoglobin (%) endpoint and less than 1% are considered significant for the vitamin B12 endpoint.

The following numerical values were used when calculating the sample size. The following are the means and standard deviations of changes in the LTG and LPG groups obtained from retrospective data analysis.

Change in hemoglobin level (%) LTG = -8.6 ± 8.5 , LPG = -3.4 ± 11.1

Total amount of vitamin B12 supplement (mg) LTG = 3.1 ± 2.2 , LPG = 0.1 ± 0.4

With a two-sided type I error of 4% (hemoglobin %) and 1% (vitamin B12), sample sizes are calculated to be 62 and 10 in each arm, respectively, to achieve 80% power. Sample size is calculated with PASS 11 (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.)

Numeric Results for the Two-Sample T-Test

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1≠Mean2

The standard deviations were assumed to be unknown and unequal.

Allocation									
Power	N1	N2	Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.80184	62	62	1.000	0.04000	0.19816	-8.6	-3.4		
8.5	11.1								
Power	N1	N2	Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.82233	10	10	1.000	0.01000	0.17767	3.1	0.1		
2.2	0.4								

(5) Sample size calculated to be N=124 (62 per arm). With a possible 10% attrition rate, a total of 138 patients (69 per arm) will need to be enrolled.

4) Subject recruitment plan

No advertisement will be posted for subject recruitment. Rather, all patients visiting the outpatient clinic who fulfill all inclusion and exclusion criteria of this clinical trial will be given priority. These patients will be provided with an explanation of this clinical trial, and signed informed consent will be obtained from those who are willing to participate. The subjects will be entered into the study by competitive enrollment.

The principal investigator and co-investigators of this study will not exclude potential patients who may be eligible to take part in this study only on the basis of race or socioeconomic status. If a patient fulfills the inclusion criteria of this study, every effort will be made to ensure the patient can take part in the study, and the investigators will have the patients understand that it is important to achieve adequate representation of all patients with proximal early gastric cancer who are receiving treatment at our institution.

Vulnerable subjects (minors/pregnant women, human fetuses, neonates/adults who lack consent capacity/students, employees/prisoners) will be excluded and will not be included in this clinical study.

11. Study procedures

1) Detailed description of study procedures

A. Standardization of surgical procedures and management of the extent of surgery

- (1) Surgeons with the following qualifications will participate in this clinical trial: surgeons who have personally performed more than fifty cases of open gastrectomy, fifty cases

of laparoscopic gastrectomy, and three cases of double tract reconstruction and work in institutions where more than 80 cases of gastrectomies are performed annually.

- (2) This is a prospective, multicenter, phase III study registered with the Korean Laparoscopic Surgical Society (KLASS) group as the KLASS-05 study following submission of a formal study proposal.
- (3) The steering committee of KLASS-05A will review an unedited surgical video of each candidate surgeon and make a decision on the final co-investigators.
- (4) Regular and ad hoc investigator meetings will be held to review the clinical trial protocol, standardize surgical techniques, and respond to unexpected side effects and results in a timely manner.

B. Study implementation and patient enrollment at participating sites

- (1) Once the study protocol is approved by the institution's IRB, the investigators can start patient enrollment after obtaining eligible patients' consent to take part in this clinical trial. Patient registration and management will be done using a web-based electronic case report form (e-CRF) provided by the Seoul National University Bundang Hospital Medical Research Collaborating Center (MRCC).
- (2) Patient enrollment procedures: once the patient is confirmed to be eligible based on all the inclusion and exclusion criteria, the patient is given an explanation of clinical trial participation and signed informed consent is obtained. Each patient's eligibility will be checked again with an enrollment eligibility checklist by accessing the web-based random assignment program provided by the Seoul National University Bundang Hospital MRCC prior to patient enrollment. The surgery will be performed after patient enrollment, and patients will be randomly assigned during surgery. The subjects will be entered into the study by competitive enrollment at each study site.
- (3) A Case report form will be completed and transferred to the data center.
- (4) For surgical quality assurance, surgical videos for every 10th case will be reviewed
- (5) Patients with proximal gastric cancer (≤ 5 cm, cT1N0M0), as determined by preoperative endoscopy, endoscopic ultrasound, CT, and biopsy results, will be randomly assigned to undergo either LPG or LTG
- (6) Considerations for patient enrollment
 - Patients will be withdrawn from the study if they decide not to take part in the study after enrollment or do not receive surgery within 30 days of enrollment.
 - If 30 days have passed since enrollment, the investigators must reevaluate the patient's enrollment criteria and obtain informed consent again in order to have the patient participate in the trial.

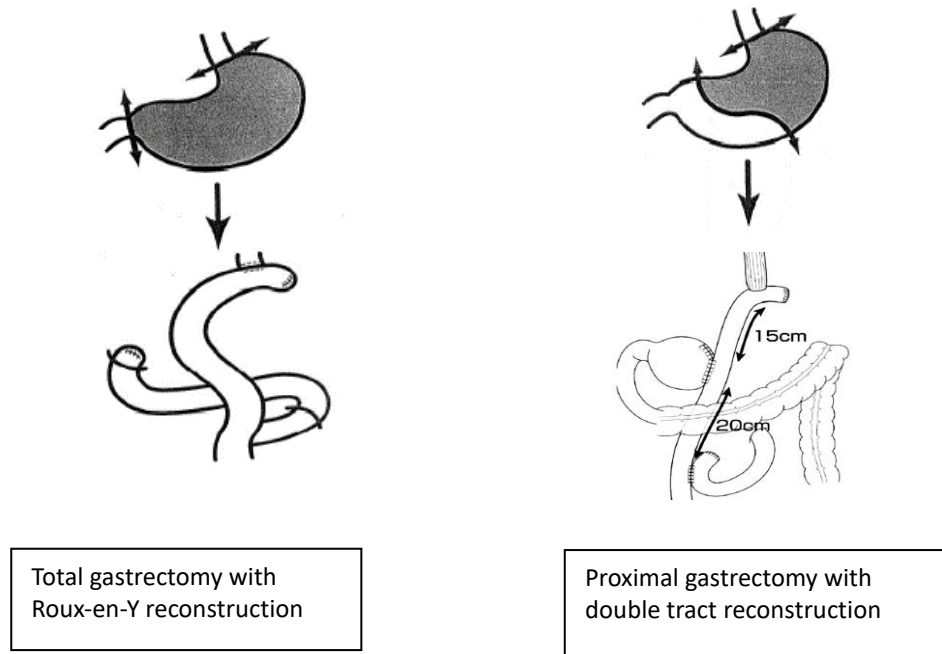
C. Treatment Plan

Arm 1: Laparoscopic total gastrectomy

Arm 2: Laparoscopic proximal gastrectomy with double tract reconstruction

- (1) In the LPG with double tract reconstruction arm, patients will undergo

laparoscopic standard radical resection consisting of proximal gastrectomy and lymphadenectomy with double tract reconstruction. In the LTG arm, patients will undergo laparoscopic standard radical resection consisting of total gastrectomy and lymphadenectomy with Roux-en-Y reconstruction.



(2) Laparoscopic proximal gastrectomy with double tract reconstruction

Under general anesthesia, the patient is placed in the reverse Trendelenburg position. The surgeon and the camera operator stand on the patient's right and the first assistant stands on the patient's left. A total of five trocars are used for the procedure. A 12-mm trocar is inserted below the umbilicus, and two 5-mm trocars are placed, one in the right and one in the left subcostal mid-axillary lines. A 12-mm trocar is inserted 2-3 cm above the umbilicus in the right mid-clavicular line, and a 12-mm trocar is inserted in the ligament of Treitz area in the left mid-clavicular line. First, a 2-0 Prolene is passed into the avascular portion of the gastrohepatic ligament for combined suture retraction of the falciform ligament and the left lobe of the liver. Partial omentectomy is started 4 cm from the gastroepiploic arcade. Due to the risk of necrosis of the greater omentum, the left gastroepiploic vessels are proximally ligated without disturbing the vessels to the greater omentum. The greater omentum is dissected to the transition zone of the lymph node stations 4d and 6, and the right gastroepiploic vessels are preserved. After dissecting the peritoneum of the upper edge of the pancreas, the lesser omentum is dissected, while preserving the right gastric vessels and the hepatic branch of the vagus nerve. The hepatic and pyloric branches of the vagus nerve should be preserved to maintain the pyloric function, the preservation of which is important for preventing delayed gastric emptying. Lymph node stations 7, 8a, and 9 are dissected, and the left gastric artery is ligated. Lymph node stations 11p and 11d are dissected along the splenic artery up to the splenic hilum. After mobilizing the esophagogastric junction portion, an intracorporeal purse-string clamp "LapJack" (Eterne, Seoul, Korea) is used to ligate the esophagus. Its distal portion is ligated with an "endo-bulldog" (B. Braun Melsungen AG, Melsungen, Germany) to prevent spillage

from the stomach. After a 2-0 Prolene suture is placed in purse-string fashion, the esophagus is transected. Next, lymph node stations 2 and 4sa are dissected by the “downstream method”. A 3-4-cm-long transverse incision is made with the extension of the left 12-mm trocar site. The stomach is taken out through this incision, and the specimen is transected with the use of linear staplers, while ensuring sufficient distal resection margin. The anvil of the circular stapler is placed in the abdominal cavity, and pneumoperitoneum is established by inserting a wound protector into the incision and sealing off the wound protector with a surgical glove. Using a laparoscopic anvil clamp, the anvil is inserted into the esophageal stump, and the purse-string suture is tied. For secure suturing, “Endo-loop” (Ethicon Endo-Surgery, Somerville, NJ) may be added to the proximal portion of the knot. The jejunum is transected 15-20 cm distal to the ligament of Treitz, and the circular stapler is inserted in the distal jejunum. Then, an end-to-side Roux-en-Y esophagojejunostomy is performed by intracorporeal anastomosis via the incision, and the jejunal stump is closed with a linear stapler. Next, side-to-side gastrojejunostomy is performed 10 cm below the esophagojejunostomy site using two linear staplers, and end-to-end jejunojejunostomy is performed 20 cm below the gastrojejunostomy site by hand-sewing suture. After checking the abdominal cavity, one or two drainage tubes (Jackson-Pratt) are placed in the esophagogastrostomy site, and the incision is closed.

(3) Laparoscopic total gastrectomy

Under general anesthesia, the patient is placed in the reverse Trendelenburg position. The surgeon and the camera operator stand on the patient’s right and the first assistant stands on the patient’s left. A total of five trocars are used for the procedure. A 12-mm trocar is placed below the umbilicus, and two 5-mm trocars are placed, one in the right and one in the left subcostal mid-axillary lines. A 12-mm trocar is inserted 2-3 cm above the umbilicus in the right mid-clavicular line, and a 12-mm trocar is inserted in the ligament of Treitz area in the left mid-clavicular line. First, a 2-0 Prolene is passed into the avascular portion of the gastrohepatic ligament for combined suture retraction of the falciform ligament and the left lobe of the liver. Partial omentectomy is started 4 cm from the gastroepiploic arcade. Due to the risk of necrosis of the greater omentum, the left gastroepiploic vessels are proximally ligated without disturbing the vessels to the greater omentum. Lymph node stations around the right gastroepiploic artery are dissected, and the vessels are ligated. Then, right gastric artery is ligated, and the duodenum is separated using a linear stapler. After dissecting the peritoneum of the upper edge of the pancreas, the lesser omentum is dissected. Depending on the location and stage of the tumor, lymph node stations 7, 8, 9, 11p, and 12a are selectively dissected, and the left gastric artery is ligated. The lymph node stations 11p and 11d are dissected along the splenic artery up to the splenic hilum. After mobilizing the esophagogastric junction portion, an intracorporeal purse-string clamp “LapJack” (Eterne, Seoul, Korea) is used to ligate the esophagus. Its distal portion is ligated with an “endo-bulldog” (B. Braun Melsungen AG, Melsungen, Germany) to prevent spillage from the stomach. After a 2-0 Prolene suture is placed in purse-string fashion, the esophagus is transected. Next, lymph node stations 2 and 4sa are dissected using the “downstream method”. A 3-4-cm long transverse incision is made by extending the left 12-

mm trocar site, and the resected stomach is taken out.

The anvil of the circular stapler is placed in the abdominal cavity, and pneumoperitoneum is established by inserting a wound protector into the incision and sealing off the wound protector with a surgical glove. Using a laparoscopic anvil clamp, the anvil is inserted into the esophageal stump, and the purse-string suture is tied. For secure suturing, “Endo-loop” (Ethicon Endo-Surgery, Somerville, NJ) may be added to the proximal portion of the knot. The jejunum is transected 15-20 cm distal to the ligament of Treitz and the circular stapler is inserted in the distal jejunum. Then an end-to-side Roux-en-Y esophagojejunostomy is performed by intracorporeal anastomosis via the incision, and the jejunal stump is closed with a linear stapler. Next, an end-to-end jejunojunctionostomy is performed 40-50 cm below the esophagojejunostomy site by hand-sewing suture through the incision. After checking the abdominal cavity, one or two drainage tubes (Jackson-Pratt) are placed in the esophagogastrostomy site, and the incision is closed.

D. Postoperative patient management

- (1) The patients taking part in this clinical trial will be managed as per patient management guidelines according to the critical pathway set by each institution, but all postoperative evaluation criteria must be assessed.
- (2) At the discretion of the investigator, mechanical lower-extremity pneumatic compression devices, compression stockings, or anticoagulants may be used pre- and postoperatively for thromboprophylaxis after surgery.
- (3) Prophylactic antibiotics used before surgery will be used after surgery for an appropriate period
- (4) At the discretion of each investigator, an imaging exam with contrast medium may be performed to check for esophagojejunostomic leakage after surgery
- (5) Postoperative diet will proceed in the order of water after fasting, liquid diet, and puree. Diet progression may be modified at the discretion of each investigator.
- (6) Appropriate pain management will be implemented; including patient-controlled analgesia (PCA), and additional analgesia may be administered if requested by the patient.
- (7) Adjuvant chemotherapy based on final pathologic finding after surgery: For stage II and stage III cancers at final pathology evaluation after surgery, 5-FU-based chemotherapy will be started within 4-6 weeks of surgery.
- (8) If patients develop anemia during the follow-up period and their hemoglobin level is less than 10g/dL, oral iron may be given as ferrous sulfate 256 mg (80 mg iron) two times a day for twelve weeks or until hemoglobin level returns to normal. If the patients do not respond well to oral iron, iron injections may be given. If iron was given, the frequency and dose must be accurately recorded.
- (9) If patients' vitamin B12 level drops below 200 pg/ml during the follow-up period, vitamin B12 injection (Actinamide 1 mg/2 ml (Cobamamide)) is intramuscularly administered, and its frequency and dose must be accurately recorded.
- (10) Two major concerns of LTG, changes in hemoglobin level and total amount of vitamin B12 supplement, will be evaluated as primary endpoints. Reflux gastrectomy, which was the most common complication after conventional LPG over the two-year study period, will be evaluated as a secondary endpoint using various methods, including endoscopy, Visick score, questionnaires, changes in

nutritional status, and upper GI series. Other secondary endpoints will include quality of life, postoperative complications and mortality rate, and survival rate (disease free survival & overall survival). These measures will be compared between the two groups to evaluate the safety, efficacy, and clinical applicability of LPG.

2) Control group selection and randomization procedures

After obtaining signed informed consent from the patients, the <subject eligibility checklist form> will be sent via fax or e-mail for patient enrollment, and individual patients will be assigned a serial number. Assignment will be given sequentially in the order the principal investigator receives the subject eligibility checklist form after obtaining informed consent from the subject. Eligible patients who fulfill all the criteria for enrollment will be randomly assigned in a 1:1 ratio to the LPG group or LTG group. Random assignment will be facilitated using the web-based random assignment at Seoul National University Bundang Hospital MRCC. Management and facilitation of randomization will be carried out by the MRCC subinvestigator, and access to and management of information on random assignment will be carried out independently from the investigators or sponsor.

3) Investigational drug administration · dose · specification, concomitant medications, rationale for selected comparator if used

Not applicable

4) Observational variables and clinical laboratory tests

- (1) Primary endpoints: change in hemoglobin level and total amount of vitamin B12 supplement at 2 years after surgery
- (2) Secondary endpoints: reflux esophagitis, quality of life, postoperative complications and mortality, and survival rate (disease free survival & overall survival)
- (3) Medical records
 - ① Informed consent form
 - ② General patient information, date of surgery, name of surgical procedure
 - ③ Preoperative diagnosis data, surgical findings, pathology results
 - ④ Postoperative patient progression record
 - ⑤ Progression monitoring after discharge record

(4) Functional evaluations

* Functional evaluations routinely performed at each institution may vary. However, blood tests, abdominal CT, endoscopic evaluation of reflux esophagitis, Visick score, EORTC-c30, sto22 and GIQLI, and physical examination must be performed at all institutions

- ① Endoscopic evaluation of reflux esophagitis (Grading according to LA classification)
 - i. (Evaluation of effects of acid or bile reflux on the esophagus)
 - ii. Endoscopy will be performed before surgery and 12 and at 24 months after surgery for gross and histological examination of the mucosa to check mucosal damage from gastroesophageal reflux and response to treatment.

② Visick score (Patient's subjective assessment of symptoms)

Table I. Visick score.

I	No symptoms, resolved
II	Mild occasional symptoms easily controlled, improved
III	Mild symptoms not controlled, unchanged
IV	Not improved, worsened

The Visick score will be used to measure patients' subjective assessment of their reflux esophagitis symptoms. It is assessed before surgery and at each visit after surgery.

③ EORTC QLQ-C30 and QLQ- STO 22 and Gastrointestinal Quality of life Index (GIQLI) questionnaires will be used to assess changes in patients' quality of life before surgery and at 3, 12, and 24 months after surgery.

④ To determine changes in nutritional status and whether there are differences between the two groups with respect to nutritional status, physical examination (weight, triceps skinfolds thickness), and blood tests will be performed before surgery and at each visit after surgery. Abdominal ultrasound will be performed before surgery and at 3, 9, and 18 months after surgery, and abdominal CT will be performed before surgery and at 6, 12, and 24 months after surgery.

⑤ Upper gastrointestinal series (UGIS)

- i. UGIS will be performed at 3, 12, and 24 months after surgery in patients undergoing proximal gastrectomy to determine the volume of the remnant stomach, effective food passage, and the effects of the lesser/greater curvature lengths of the remnant stomach on reflux esophagitis.

⑥ Gastric emptying scan

A gastric emptying scan will be performed at 3, 12, and 24 months after surgery in patients undergoing proximal gastrectomy to determine effective food passage without delayed gastric emptying in the remnant stomach.

⑦ Visit plan and schedule

Table II. Study flow sheet

Procedure	Screening /Baseline ¹	Surgery	Postoperative Day 1 ~ Discharge	Postoperative Day 25	Postoperative months 3~ 24	Study completion/early termination
Visit Day		0			Postoperative months 3,6,9,12,18, and 24	

¹ Screening test is to be completed ≤ 3 months before surgery.

Visit window		±14 days	±30 days	
Informed consent ²	V			
Inclusion and exclusion criteria verification	V			
Randomization ³		V		
Medical history, ASA, ECOG	V			
Visick score	V	V	V	
Weight/ Triceps Skinfoldds Thickness	V	V	V	
Complete blood cell count	V		V	
Chemistry	V		V	
Blood coagulation test	V			
Tumor marker test ⁴	V		V	
Abdominal CT	V		V ⁵	
Upper endoscopy	V		V ⁶	
Abdominal ultrasound	V		V ⁷	
UGIS			V ⁸	
Gastric emptying scan			V ⁹	
Surgery		V ¹⁰		
Recovery evaluation after surgery ¹¹		V		
Early complication check		V	V	
Late complication check			V	
Pathology result check		V		
EORTC-c30, sto22 and GIQLI questionnaires ¹²	V		V	
Recurrence and survival check			V	V
Case conclusion				V

5) Efficacy evaluation criteria and methods

The following variables will be measured in order to evaluate the efficacy of LPG and LTG with double tract reconstruction in patients with preoperative stage 1 proximal gastric cancer.

- (1) Changes in hemoglobin level and total amount of vitamin B12 supplement after LTG or LPG with double tract reconstruction
- (2) Comparison of quality of life after LTG and LPG with double tract

² If surgery cannot be performed because > 30 days have passed since obtaining informed consent, re-consent process is done.

³ Randomization is to be performed during surgery after all screening assessment results have been confirmed.

⁴ Tumor marker test includes CEA, CA19-9, and α FP.

⁵ Abdominal CT is to be performed before surgery and at 6, 12, and 24 months after surgery (if done at another hospital, the date on which it was performed at that hospital should be recorded)

⁶ Upper endoscopy is to be performed before surgery and at 12 and 24 months after surgery.

⁷ Abdominal ultrasound is to be performed before surgery and at 3, 9, and 18 months after surgery.

⁸ UGIS is to be performed at 3, 12, and 24 months after surgery for patients in the proximal gastrectomy group.

⁹ Gastric emptying scan is to be performed at 3, 12, and 24 months after surgery for patients in the proximal gastrectomy group.

¹⁰ Surgery is performed according to randomization during surgery.

¹¹ Diet progress and discharge status are checked.

¹² EORTC-c30, sto 22, GIQLI questionnaires are only to be completed before surgery and at 3, 12, and 24 months after surgery.

reconstruction

- (3) Cost-effectiveness analysis after LTG or LPG with double tract reconstruction
- (4) Oncologic outcome analysis after LTG or LPG with double tract reconstruction

6) Differences with the conventional treatment and previous studies

Open or LTG is considered the conventional treatment for upper third early gastric cancer. Compared to these conventional treatments, LPG with double tract reconstruction is a minimally invasive surgical technique with a focus on function preservation.

Most previous studies on this subject were retrospective studies based on only a few patients. This is the first prospective, multicenter, randomized clinical trial to seek medical evidence for proximal gastrectomy with double tract reconstruction.

7) Benefits and risks to the subjects

This is not a study comparing a new surgical technique with the conventional technique, but a prospective, multicenter, randomized study on conventional surgical techniques, and as such these techniques are not expected to have high risks. However, because quality control will be needed for co-investigators who are not experienced in LPG with double tract reconstruction, one unedited surgical video will be reviewed prior to surgeon's participation in the study and unedited video for every 10th surgery will be additionally reviewed to minimize subject risk.

8) Criteria for cessation · withdrawal

- (1) All surgeries will be carried out laparoscopically. All cases of conversion to open surgery will be withdrawn.
- (2) Subjects excluded based on surgical findings
If the investigator deems gastrectomy and lymphadenectomy are not prudent or impossible based on the laparoscopic surgery findings, the patient will not receive the surgical procedure and will be withdrawn from this clinical trial. In addition, the patient will be withdrawn from the trial if serosal invasion or lymph node metastasis at the splenic hilum is suspected.

9) Safety evaluation criteria, including side effects, and evaluation and reporting methods

To evaluate the safety of LTG and LPG, reconstruction methods, and lymphadenectomy, the following variables will be measured.

- (1) Early complications within 30 days of surgery will be compared between the patients who received LTG and lymphadenectomy and those who received LPG with double tract reconstruction and lymphadenectomy.
- (2) Postoperative bowel recovery, diet initiation, and length of hospital stay of the patients who received LTG and lymphadenectomy those who received LPG with double tract reconstruction and lymphadenectomy.
- (3) Surgical outcomes (intra- and post-operative complications, anastomosis time, anastomosis success rate, and conversion rate to open surgery) will be compared between the LTG with Roux-en-Y reconstruction and LPG with double tract reconstruction groups.

① Serious Adverse Events (SAE)

Serious Adverse Events (SAE) are defined as follows.

- A. All deaths within 90 days of surgery
 - Must be reported as a SAE whether or not it has a causal relationship with the surgery
- B. Permanent or significant disability that has an evident causal relationship to surgery regardless of study phase (including permanent brain lesions)
- C. When the following treatments are given due to problems determined to have a causal relationship to early postoperative complications (causal relationship with early complications will be classified as definite, probable, and possible for reporting)
 - Reoperation at the present or other institution due to early complications after surgery
 - Unplanned treatment in the intensive care unit of the present or other institution due to early complications after surgery

* Reoperation: surgery in an operating room requiring general anesthesia

② Adverse Event Reporting

- A. In case of an adverse event, the treating doctor or institution's coordinator who becomes aware of the event must report to the principal investigator. If the principal investigator is unreachable, the treating doctor or institution's coordinator must act on behalf of the principal investigator and carry out his/her responsibilities.
- B. The institution's principal investigator or acting principal investigator must document the event on Serious Adverse Event Report Form (SAE Report) and report it to the study chair within 24 hours he/she becomes aware of the event, and the study chair will report it to the steering committee.
- C. The steering committee will decide the urgency, significance, and degree of impact of the event. If necessary, the steering committee can stop enrollment temporarily after notifying the study sites and discuss the stopping the study

10) Data Safety Monitoring Plan (DSMP)

- (1) Monitoring director: Study Chair (Do Joong PARK, Professor, Department of Surgery, Seoul National University College of Medicine)
- (2) The investigator or clinical research coordinator will send <Subject Eligibility Checklist Form> to the principal investigator via e-mail prior to enrollment. Case report form <CRF-1>, which includes patient data until the subject's discharge, will be delivered via mail to the principal investigator. <CRF-2>, which includes patient data from discharge to study completion (30 days after surgery), will be delivered via mail to the principal investigator. If the CRC completes CRFs, the investigator will review the completed CRFs each time.

(CRF should be addressed to)

E-mail: djpark@snuh.org, Phone:010-3079-7099

(Mail) Do Joong PARK, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul, Republic of Korea 03080

(3) Monitoring Plan

- Monitoring by the principal investigator or an independent body on a regular basis: monitoring visit is scheduled for every 30 cases and every 6 months. Monitoring of surgical video will be done for every 10 cases. SAE: monitoring will be performed for every 5 cases of $\geq$ Clavien-Dindo classification grade IIIa. Unexpected adverse events, problems, and protocol deviations must be immediately reported to the principal investigator and IRB after the investigator becomes aware of the event. If the principal investigator determines the event is a serious problem or recommendation is given by the IRN, an ad hoc investigator meeting must be immediately held to evaluate the event.
- Efficacy variable monitoring for continuation, modification, and discontinuation of the study:
If results from regular monitoring (every 30 cases and every 6 months) shows significant differences in changes in hemoglobin level, quality of life index, surgery-related complications, and oncologic safety between the two groups, this finding must be immediately reported to the principal investigator, and the principal investigator must hold an ad hoc investigator meeting as soon as possible upon receiving such report to conduct an evaluation of this finding.

11) Data and Statistical Analysis Methods

(1) Analysis populations

A. Efficacy analysis populations

■ Intention to treatment (ITT) population

- All patients randomized to each arm who are not included in the below criteria after participating in this trial.
- i. Patients who did not undergo resection due to metastasis found after diagnostic laparoscopy

■ Per-protocol (PP) population

- Per-protocol (PP) population excludes the following patients.
- i. Patients who received a different surgical procedure than they were randomized to based on the investigator's decision or patient characteristics (including conversion from laparoscopic to open surgery and conversion from proximal gastrectomy to total gastrectomy)
- ii. Patients who received combined resection of other surrounding organs or gastrectomy other than proximal gastrectomy or total gastrectomy during surgery due to various reasons.
- iii. Patients who have undergone anticancer therapy after surgery
- iv. Violation of inclusion, exclusion criteria

If the difference between the ITT and PP populations is $\geq 10\%$, the analysis will be based on the ITT population for the study's purpose.

B. Safety analysis populations

- Safety analysis, including postoperative complications and mortality rate, of all subjects who received treatment according to their procedure. This population will be divided into experimental and control groups and will be compared, excluding those who did not receive any procedure

(2) Analysis primary efficacy endpoints

- A. Changes in hemoglobin level and total amount of vitamin B12 supplement at 2 years after surgery

B. Independent t test will be performed to assess the superiority of the LPG group versus the LTG group in terms of changes in hemoglobin level and total amount of vitamin B12 supplement at 2 years after surgery. All statistical tests will be performed at statistical significance level of 5% unless otherwise noted. Because the sample size is calculated by the power requirement of the primary efficacy endpoints, power for secondary endpoints cannot be guaranteed.

(3) Analysis secondary efficacy endpoints

A. Reflux esophagitis

- Chi-square test (or Fisher's exact test) will be performed to evaluate differences in endoscopic evaluation of reflux esophagitis (endoscopic LA classification) and Visick scores between the two groups.

B. Quality of life

- Quality of life (EORTC-C30 and STO22) before surgery and at 6, 12, 24, and 36 months after surgery will be analyzed as follows:

- For the EORTC-C30, separate analysis will be performed for the five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, pain and nausea, and vomiting), one global health status, and six single items

- For the EORTC-STO22, separate analysis will be performed for the five gastric cancer-related scales (dysphasia, eating restriction, pain, reflux, and anxiety) and four single items (dry mouth, body image, taste and hair loss)

- Because the data collected will be repeated measures over time, analysis will be performed using multilevel mixed-effects linear regression models to examine whether there are differences in quality of life between the LPG and LTG groups

C. Postoperative complications and mortality rate

- Chi-square test (or the Fisher's exact test) will be performed to evaluate differences in early and late postoperative complications and in the 90-day mortality rate between the two groups.

D. Analysis of oncologic outcomes

- Disease-free survival rate

The time from randomization to recurrence (or death) will be estimated using the Kaplan-Meier Method. For patients with recurrence, time from the randomization to recurrence (or death) will be considered, and for censored patients, time from randomization to censored point will be considered. The log-rank test will be performed to compare disease-free survival rate between the two groups.

- Overall survival rate

The time from randomization to death will be estimated using the Kaplan-Meier Method. For patients who are dead, time from the randomization to death will be considered, and for censored patients, time from randomization to censored point will be considered. The log-rank test will be performed to compare overall survival rate between the LPPG and LDG groups.

12) Study calendar

Category	Total study duration (2016 ~ 2020)							
	1 st year		2 nd year		3 rd year		4 th year	
	1/1	2/1	1/2	2/2	1/3	2/3	1/4	2/4
Promote multicenter participation and investigator meeting								
Web-based database building								
Co-investigator selection, establishment of standard surgical technique								
Competitive subject enrollment and data collection								
Data accumulation and presentation of surgical outcome								

12. Measures for subject safety and protection

1) General plan for research ethics

Few studies have reported that total gastrectomy is beneficial for patient prognosis in proximal gastric cancer, but most of these studies have included a large number of patients who had oncologic characteristics to metastasize to other parts of the body, which makes it hard to generalize the results of these studies. We believe that if patients are selected based on the above-mentioned oncologic criteria, there will be no differences in long-term survival between the group that undergoes LTG and the group that undergoes LPG for proximal gastric cancer. We will conduct this study in strict accordance with the most recent version of Declaration of Helsinki (2013th edition) and will obtain approval from the IRB before initiating the study. This will selectively apply to patients with proximal gastric cancer who meet the above-mentioned oncologic factors. In the event of an unexpected side effects or results, patients' safety will be the first priority when responding to these matters, and a reevaluation of the study will be performed.

2) Informed Consent Procedures

- (1) The investigator will provide explanation to and obtain consent from subjects: co-investigators or sub-investigators listed in this study protocol may also provide information and gain consent.
- (2) Person providing the consent: subjects or their representative (subjects in principle)
- (3) Waiting period between imparting study information and requesting informed consent: will be decided by the subject. However, the subject will be excluded from the study if he/she cannot make the decision until one week after the initial explanation or before the surgery
- (4) Methods to minimize the possibility of coercion or unjustified effect: there will be no additional benefit of any kind related to this clinical trial or any differences in treatment. With regard to this, subject monitoring will be routinely conducted and will be immediately reported to the IRB
- (5) Language used by the investigator when providing explanation of the study and obtaining informed consent: Korean. Therefore, subjects who are not familiar with Korean and cannot understand the study in its entirety will be excluded.
- (6) Language understood by subjects or their representative: Korean. Therefore, subjects who are not familiar with Korean and cannot understand the study in its entirety will

be excluded

- (7) Information and consent form provided to the subjects and their representative:
A copy of IRB-approved informed consent form will be provided to the subjects

3) Subject compensation

- (1) Incentives and compensations provided to subjects: none
- (2) If a surgery-related injury occurs during the trial, appropriate treatment will be provided and every effort will be made for recovery from the side effects and minimize the cost the patient needs to pay if hospitalization is required.
- (3) The institute will provide necessary treatments for the recovery from side effects that arise. However, the subjects will be responsible for the cost of inpatient or outpatient treatment for side effects from the surgery and medical expenses not related to this study.

4) Personal information protection plan

- (1) The patient's medical record number and pathology number will be kept in separate folders for each patient under the responsibility of the principal investigator. This information will be codified so that personal information is not identifiable. In addition, study data will be saved in a password-protected file and kept in a laboratory with a lock.
- (2) In accordance with Article 15 of the Enforcement Regulations of the Bioethics Act, study-related records must be retained for a period of 3 years following the study completion. After the retention period, the documents are destroyed according to Article 16 of the enforcement ordinance of the Personal Information Protection Act. However, the investigator must report to the IRB if records must be retained for longer than 3 years for follow-up studies, registers, data accumulation, etc.

5) Additional safeguards for protecting vulnerable populations if included

Vulnerable subjects are excluded from the study for the protection of subjects

13. Storage and disposal of human biological materials

Not applicable

14. References

1. Kobayashi T, Sugimura H, Kimura T. Total gastrectomy is not necessary for proximal gastric cancer. *Dig Surg*. 2002; 19: 15-21.
2. Kondoh Y, Okamoto Y, Morita M, et al. Clinical outcome of proximal gastrectomy in patients with early gastric cancer in the upper third of the stomach. *Tokai J Exp Clin Med*. 32; 2: 48-53.
3. Jin L, Yoshida M, Kitagawa Y, et al. Subclassification of superficial cardia cancer in relation to the endoscopic esophagogastric junction. *J Gastroenterol Hepatol*. 2008; 23(Suppl 2): S273-7.
4. Weitz J, Brennan M, Karpeh M. Association of splenectomy with postoperative complications in patients with proximal gastric and gastroesophageal junction cancer. *Ann Surg Oncol*. 2004; 11: 682-9
5. Hyung WJ, Lim JS, Song JW, et al. Laparoscopic spleen-preserving splenic hilar lymph node dissection during total gastrectomy for gastric cancer. *J Am Coll Surg*. 2008; 207: e6-11
6. Maruyama K, Sasako M, Kinoshita T, et al. Pancreas-preserving total gastrectomy for

- proximal gastric cancer. *World J Surg* 1995; 19: 532-536.
7. Shin SH, Jung H, Choi SH, et al. Clinical Significance of splenic hilar lymph node metastasis in proximal gastric cancer. *Ann Surg Oncol*. 2009; 16: 1304-9.
 8. Monig SP, Collet PH, Baldus SE, et al. Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus . *J Surg Oncol*. 2001; 76: 89-92.
 9. Csendes A, Burdiles P, Rojas J, et al. A prospective study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. *Surgery*. 2002; 131: 401-7.
 10. Kitamura K, Yamaguchi T, Nishida S, et al. The operative indications for proximal gastrectomy in patients with gastric cancer in the upper third of the stomach. *Surg Today*. 1997; 27: 993-8.
 11. Kobayashi T, Sugimura H, Kimura T. Total gastrectomy is not always necessary for advanced gastric cancer of the cardia. *Dig Surg*. 2002; 19: 5-21.
 12. Kunisaki C, Akiyama H, Nomura M, et al. Surgical outcomes for early gastric cancer in the upper third of the stomach. *J Am Coll Surg*. 2005; 200: 15-9.
 13. Kondoh Y, Ishii A, Ishizu K, et al. Esophagogastrectomy before proximal gastrectomy in patients with early gastric cancers in the upper third of the stomach. *Tokai J Exp Clin Med*. 2006; 31: 146-9.
 14. 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: 587-91.
 15. Sakuramoto S, Yamashita K, Kikuchi S, et al. Clinical Experience of Laparoscopy Assisted Proximal Gastrectomy with Fundoplication in EGC for preventing Reflux Esophagitis. *J Am Coll Surg*. 2009; 209: 344-51.
 16. Tokunaga M, Ohyama S, Hiki N, et al. Endoscopic evaluation of reflux esophagitis after proximal gastrectomy comparison between EG anastomosis and jejunal interposition. *World J Surg*. 2008; 32: 1473-7.
 17. Adachi Y, Katsuta T, Aramaki M, et al. Proximal gastrectomy and gastric tube reconstruction for early cancer of the gastric cardia. *Dig Surg*. 1999; 16: 468-70.
 18. Iwahashi M, Nakamori M, Nakamura M, et al. Evaluation of double tract reconstruction after total gastrectomy in patients with gastric cancer prospective randomized controlled trial. *World J Surg*. 2009; 33: 1882-8.
 19. Takeshita K, Saito N, Saeki I, et al. Proximal gastrectomy and jejunal pouch interposition for the treatment of early cancer in the upper third of the stomach: Surgical techniques and evaluation of postoperative function. *Surgery*. 1997; 121: 278-86.
 20. Adachi Y, Inoue T, Hagino Y, et al. Surgical results of proximal gastrectomy for early-stage gastric cancer: Jejunal interposition and gastric tube reconstruction. *Gastric Cancer*. 1999; 2: 40-5.
 21. Shiraishi N, Adachi Y, Kitano S, et al. Clinical outcome of proximal versus total gastrectomy for proximal gastric cancer. *World J Surg*. 2002; 26(9): 1150-4.
 22. Yoo CH, Sohn BH, Han WK, Pae WK. Analysis of local recurrence following proximal gastrectomy in patients with upper third gastric cancer. *Cancer Res Treat*. 2002; 34: 247-51.
 23. Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Long-term outcome after proximal gastrectomy with jejunal interposition for suspected early cancer in the upper third of the stomach. *Br J Surg*. 2010; 97: 558-62.
 24. Yumiba T, Kawahara H, Nishikawa K, et al. Impact of esophageal bile exposure on the genesis of reflux esophagitis in the absence of gastric acid after total gastrectomy. *Am J Gastroenterol*. 2002; 97: 1647-52.
 25. Ahn SH, Jung DH, Son SY, et al. Laparoscopic double-tract proximal gastrectomy for proximal early gastric cancer. *Gastric Cancer* 2013;

Statistical Analysis Plan

Multicenter prospective randomized controlled trial comparing laparoscopic proximal gastrectomy and laparoscopic total gastrectomy for upper third early gastric cancer (KLASS-05)

(4) Analysis populations

C. Efficacy analysis populations

■ Intention to treatment (ITT) population

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- ii. Patients who did not undergo resection due to metastasis found after diagnostic laparoscopy

■ Per-protocol (PP) population

- Per-protocol (PP) population excludes the following patients.
- v. Patients who received a different surgical procedure than they were randomized to based on the investigator's decision or patient characteristics (including conversion from laparoscopic to open surgery and conversion from proximal gastrectomy to total gastrectomy
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- vii. Patients who have undergone anticancer therapy after surgery
- viii. Violation of inclusion, exclusion criteria

If the difference between the ITT and PP populations is $\geq 10\%$, the analysis will be based on the ITT population for the study's purpose.

D. Safety analysis populations

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- B. Independent t test will be performed to assess the superiority of the LPG group versus the LTG group in terms of changes in hemoglobin level and total amount of vitamin B12 supplement at 2 years after surgery. All statistical tests will be performed at statistical significance level of 5% unless otherwise noted. Because the sample size is calculated by the power requirement of the primary efficacy endpoints, power for secondary endpoints cannot be guaranteed.

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- Because the data collected will be repeated measures over time, analysis will be performed using multilevel mixed-effects linear regression models to examine whether there are differences in quality of life between the LPG and LTG groups

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- Chi-square test (or the Fisher's exact test) will be performed to evaluate differences in early and late postoperative complications and in the 90-day mortality rate between the two groups.

D. Analysis of oncologic outcomes

- Disease-free survival rate

The time from randomization to recurrence (or death) will be estimated using the Kaplan-Meier Method. For patients with recurrence, time from the randomization to recurrence (or death) will be considered, and for censored patients, time from randomization to censored point will be considered. The log-rank test will be performed to compare disease-free survival rate between the two groups.

- Overall survival rate

The time from randomization to death will be estimated using the Kaplan-Meier Method. For patients who are dead, time from the randomization to death will be considered, and for censored patients, time from randomization to censored point will be considered. The log-rank test will be performed to compare overall survival rate between the LPPG and LDG groups.