Supplementary Online Content 1

Protocol

Title: Multi-institutional prospective randomized trial for effectiveness assessment of laparoscopic surgery for clinical stage I gastric cancer

1. Title of Research

Multi-institutional prospective randomized trial for effectiveness assessment of laparoscopic surgery for clinical stage I gastric cancer

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4. Purpose and Background of Clinical Trials

4.1 Purpose of Clinical Trials

1) Primary Endpoint

The purpose of this clinical trial is to verify that the 5-year overall survival rate of laparoscopic distal subtotal gastrectomy is non-inferior to open distal subtotal gastrectomy in the treatment of clinical stage I gastric cancer.

2) Secondary Endpoints

Disease-free survival and recurrence

Morbidity (Early postoperative morbidity defined as complications that occur within thirty days after surgery/ Late postoperative morbidity defined as complications that occur after postoperative day 30) and mortality

Quality of life

Inflammation and immune response

Cost-effectiveness

4.2 Background of Clinical Trials

1) Epidemiology of gastric cancer

Gastric cancer, the most prevalent type of cancer in Korea, accounts for 20.2% of all cases of cancer according to a 2002 report by the Korea Central Cancer Registry Program. In 2001, Statistics Korea associated gastric cancer with the second highest mortality rate, trailing behind lung cancer. It is known as the cause of death for 24 in every 100,000 Koreans.

2) Increase in early gastric cancer

The introduction of endoscopy has led to a significant increase in the diagnosis of early gastric cancer. According to a report by the Korean Gastric Cancer Association, the proportion of early gastric cancer rose from 28.6% in 1995 to 32.8% in 1999.[1] This trend was more prominent in the case of Japan, with a 2000 study by Maehara et al. showing an increase in the proportion of early gastric cancer from 18% to 57% in the past twenty years. Early gastric cancer refers to invasive gastric cancer that invades no more deeply than the submucosa, regardless of lymph node metastasis. Curative resection is possible in most cases, and if performed, at least 95% of patients achieve long-term survival without recurrence. The General Surgery Department of Seoul National University Hospital observed 1,452 patients who had received curative resection for early gastric cancer from 1986 to 1995, and reported a 5-year recurrence rate of 1.8%, which is equivalent to 26 patients.[2] Following the successful treatment of early gastric cancer, research on surgical procedures has begun to focus on the improved survival rate and the quality of life (QOL) of patients.[3]

3) Treatment of early gastric cancer

The prognosis of gastric cancer depends on the depth of invasion through the stomach wall and lymph node metastasis. Early gastric cancer refers to cancer in which invasion has occurred no more deeply than the submucosa. The possibility of lymph node metastasis, usually limited to level I lymph nodes, is 4% for tumors confined to the mucosa and 20% in the case of submucosal infiltration. Recommended surgical

procedures are subtotal gastrectomy for two-thirds of the stomach, total gastrectomy or dissection of level II lymph nodes. In other words, about 80% of patients suffering from early gastric cancer undergo more intensive surgeries that necessary.

4) Development of laparoscopic surgery

Laparoscopic gastrointestinal surgery was first introduced in 1991 with laparoscopic Nissen fundoplication.[4,5] For gastric cancer, Ohgami et al. attempted laparoscopic wedge resection in 1992,[6] and Kitano et al. employed laparoscopy-assisted gastrectomy including lymphadenectomy in 1994.[7] In the mid-1990s, laparoscopic gastrointestinal surgery grew more widespread due to improved surgical procedures, development of surgical tools, and a greater interest in patients' QOL among surgeons. Recently, Korea has also seen a surge in laparoscopic gastrointestinal surgery. According to a report by the Information Committee of the Korean Gastric Cancer Association and the Korean Laparoendoscopic Gastrointestinal Surgery Study Group, the total cases of laparoscopic gastrointestinal surgery in Korea were 70 in 2000, 209 in 2001, 328 in 2002, 539 in 2003, and 1,005 in 2004 (Fig. 1).[8] This steady increase can be attributed to the employment of laparoscopic surgery in the treatment of malignant diseases. Among the aforementioned cases, malignant diseases accounted for 87 in 2001, 181 in 2002, 405 in 2003, and 701 in 2004 (Fig. 2).

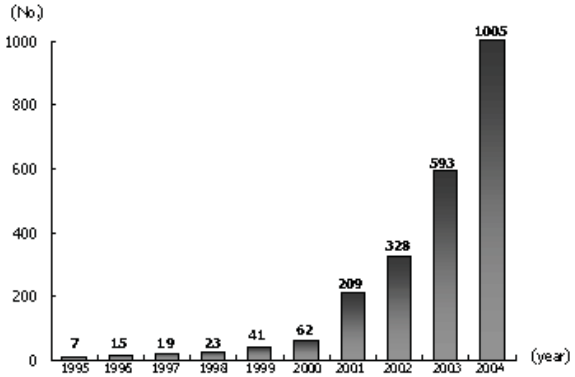

Figure 1. The number of total cases of laparoscopic gastrointestinal surgery in Korea

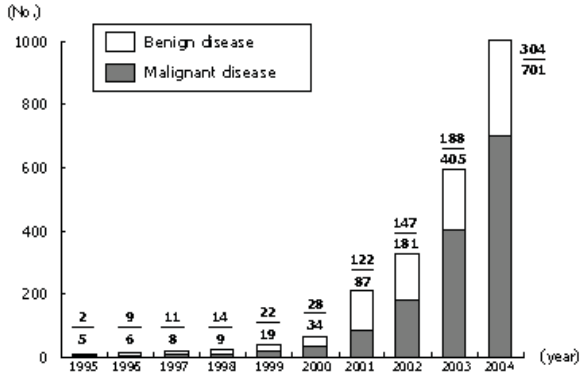

Figure 2. Laparoscopic gastrointestinal surgery in Korea according to benign and malignant disease

5) Problems

Given the lack of scientific evidence on the superiority of laparoscopic surgery, the increase in laparoscopic gastrointestinal surgery may be the result of surgeons' efforts to keep up with the changing times. Given the high cure rate of at least 90% using current methods, extra caution must be exercised when presenting a new surgical procedure for early gastric cancer. More objective and scientific evidence is required on the standardization of laparoscopic surgical procedures, the stability of laparoscopic surgery, recurrence and survival rates, QOL after laparoscopic surgery, and surgical costs.

6) Significance of research in Korea

Active research is being conducted on the advantages offered by laparoscopic surgery in the treatment of gastric cancer, but most studies are retrospective, and the handful of prospective studies have only been performed on small groups. Large-scale, multi-institutional, prospective, randomized research on the short-term benefits and long-term survival of laparoscopic surgery for gastric cancer has not been attempted.[9-12] If Korea pursues multi-institutional, large-scale, prospective, randomized research in this field, it will be the first of its kind in the world. Since Korea and Japan have seen greater success in the treatment of gastric cancer than the West, the prospective, randomized research by surgeons with extensive experience in laparoscopic surgery for gastric cancer is expected to produce highly significant results.

7) Feasibility and validity

The doctors participating in this study specialize in gastric surgery, and the general surgeons have performed open gastrectomy and laparoscopic gastrectomy at least 50 times each. The affiliated hospitals treat more than 80 cases of gastric cancer in a year. In addition to the retrospective analysis, the results of laparoscopic gastrectomy performed by the participating surgeons were analyzed as a preliminary study. Out of the 723 patients, 612 (84.6%) suffered from early gastric cancer and 111 (15.4%) from advanced gastric cancer. By gender, there were 437 males and 286 females. The patients had an average age of 56.4 (24-87) and an average body mass index of 23.3 (13.9-36.2) kg/m^2. Total gastrectomy was performed for 72 (10.0%) patients, distal subtotal gastrectomy for 638 (88.2%), and proximal gastrectomy for 13 (1.8%). After the gastrectomy, B-I was performed for 464 (64.2%) patients, B-II for 143 (19.8%), Roux-en Y for 103 (14.2%), and esophagogastrostomy for 13 (1.8%). The average time spent on surgery was 226.8 (90-520) minutes, and the number of dissected lymph nodes averaged to 30.7 (6-84). Under the UICC stage classification, there were 558 (77.2%) patients in stage Ia, 102 (14.1%) in Ib, 46 (6.4%) in II, 14 (1.9%) in IIIa, 2 (0.3%) in IIIb, and 1 (0.1%) in IV. The incidence of post-surgery complications and mortality were 13.0% (94 cases) and 0.6% (4 cases), respectively. Wound infection was the most common at 4%, followed by intra-abdominal bleeding at 2.2%, intra-abdominal abscess at 1.6%, gastrointestinal bleeding

at 1.2%, anastomotic leakage at 1.1%, intestinal obstruction at 0.8%, and anastomotic stricture at 0.6%. The time taken to pass gas after surgery was 3.3 days on average, and the average length of stay for patients without post-surgery complications was 8.0 days. A follow-up study was performed on 708 (98%) out of 719 patients, with the exception of the four deaths caused by surgery. Three patients had died from diseases other than gastric cancer, and one from the recurrence of gastric cancer. A total of eight patients developed recurrence, with three in the peritoneum, and one each in the lymph nodes, bones, ovary, remnant stomach and port site. One of the patients with recurrence in the peritoneum, and those with recurrence in the bones and ovary had been diagnosed with advanced gastric cancer. The remaining were early gastric cancer patients. The results indicate that the procedure is likely to be effective in the treatment of early gastric cancer if carefully performed by general surgeons with extensive experience in laparoscopic gastrectomy. This will be presented in the upcoming June congress of the European Association for Endoscopic Surgery. The implementation of this multi-institutional, prospective research to develop and standardize laparoscopic surgical procedures for gastric cancer based on comparisons with open gastrectomy in terms of standardization process, stability of surgical procedures, post-surgery recurrence, survival rates, QOL after surgery, and surgical costs will not only contribute to the standardization of gastric cancer treatment and QOL of gastric cancer patients, but also lower the medical costs involved. The research will lead to qualitative improvements in the treatment of gastric cancer patients and provide measures to effectively lower the related medical costs.

5. Target diseases and subjects

5.1 Selection criteria

1) A patient aged between 20 to 80 years old

2) Pathologically proven gastric adenocarcinoma based on endoscopic evaluation

3) ASA (American society of anesthesiology) score I – III

4) ECOG PS (Eastern cooperative oncology group performance status) 0 or 1

5) Preoperative stage of cT1N0M0, cT1N1M0, and cT2aN0M0 according to American Joint Committee on Cancer/Union for International Cancer Control 6th edition

6) A patient deemed fit for subtotal gastrectomy

7) A patient who has provided consent for participation (or a patient whose guardian has provided consent) after receiving general instructions

5.2 Exclusion criteria

1) A patient with a history of gastrectomy

2) A patient who has received radiotherapy, immunotherapy or chemotherapy for cancer in another organ before being diagnosed with gastric cancer

3) A patient with active synchronous double cancer (suffering from cancer in another organ)

4) A patient who has received treatment for systemic inflammatory disease before surgery

5) A patient who has participated in other clinical tests in the past six months, or is still participating in such tests

6) A patient considered vulnerable (One who is incapable of adequate communication, one who is pregnant or plans to be pregnant)

7. Number of research subjects and basis of calculation

7.1 Number of research subjects

The number of required cases is 1400 (700 cases of laparoscopic gastrectomy and 700 cases of open gastrectomy).

7.2 Basis of calculation

This study calculates the effective number of subjects based on the 5-year overall survival rate after open gastrectomy. The assumptions are listed below.

1) Significance level α=0.05

2) Type II error (β) is set as 0.20 to maintain a power of 80%.

3) The number of open gastrectomy cases is the same as the number of laparoscopic gastrectomy cases. [n1 (number of open gastrectomy cases) = n2 (number of laparoscopic gastrectomy cases)]

4) Based on previous literatures, the 5-year overall survival rate (p1) of open gastrectomy is presumed to be 90%. The same is assumed for laparoscopic gastrectomy (p2). In this study, we set the non-inferiority margin at 5% (non-inferiority test).

5) *H0: p1-p2≤δ vs H1: p1-p2>δ*

6) The survival functions of both groups follow an exponential, and proportional hazards is assumed.

** Calculation process

- Non-inferiority margin of 5%
  The survival function of open gastrectomy and laparoscopic gastrectomy is $S1(t)=\exp(-\lambda 1t)$ and $S2(t)=\exp(-\lambda 2t)$ respectively. Since the ratio of hazards between the two groups is $\Delta 0=\ln(0.85)/\ln(0.9)=1.5403$. The null hypothesis and alternative hypothesis are as follows.
- H0: $\Delta \geq \Delta 0$ vs. H1: $\Delta < \Delta 0$
- Assuming n1=n2, the proportion of patients in each group represented by p1 and p2 is 0.5, the patient registration period a is 2.5 years, the follow-up observation period b is 5 years, and the common hazards rate of the two groups under the alternative hypothesis is $\lambda = -1/5\ln(0.85)=0.0325$.
- Formula

$$D=\frac{[\sqrt{\Delta_0}z_{1-\alpha}+(p_1+p_2\Delta_0)z_{1-\beta}]^2}{p_1p_2(\Delta_0-1)^2}$$

$$d=1-\frac{\exp(-\delta\lambda)}{a\lambda}[1-\exp(-a\lambda)]$$

The number of patients required in each group is n=D/d.

Target number (Unit: persons)	Laparoscopic	Open	Total
Final number of subjects	633	633	1266
Number of subjects including withdrawal rate (10%)	700	700	1400

8. Clinical trial methods

8.1 Conditions for participating surgeons and standardization of surgery

The surgeons participating in the trial were to have conducted at least 50 cases each of LADG and ODG, and each participant's institution was to conduct at least 80 cases each year for surgical quality control. We established a standardized protocol of the procedure, and all of the surgeons' operation quality was assessed by 2 experienced surgeons' site visits. Then, all of the participating surgeons thoroughly reviewed each other participant's unedited videos for the standardization and quality control of the study.

To apply standardized procedures to all aspects of the surgery, video-based reviews and discussions will continue to be held after the start of clinical trials. Video recordings will be made for all laparoscopic surgery, and field photos will be taken after gastrectomy in the case of open surgery.

8.2 Institutional participation and patient registration

1) Patient registration will begin after obtaining approval from the institutional review board of affiliated institutions.

2) Method of patient registration

General instructions on clinical trials are provided to obtain informed consent from patients who satisfy all selection criteria and none of the exclusion criteria. A researcher of Seoul National University Bundang Hospital, the principal institution, reviews the eligibility of selected subjects before registration and randomization.

3) Considerations for registration

① Patients are rejected if they refuse to participate after registration or do not undergo surgery within 30 days of registration.

② For patients to participate in clinical trials after the 30-day limit, they must be reassessed according to the initial registration criteria and provide consent again.

4) Completion period

Registration will end when the number of randomized, registered subjects reaches 1,400.

5) Randomization method

A randomized table prepared by an independent data management group was used, and 60 codes are assigned by institution and researcher. Randomization is performed such that each researcher is assigned to one subject, and block randomization is carried out. The size of blocks remains undisclosed to researchers.

Two copies of the randomization table are made, and each stored by the researcher and the data management group. Research subjects are randomly assigned to the control group or test group, and the monitors of each institution are kept informed.

8.4 Treatment details and collection of results

Histopathological details determined based on pre-surgery records, surgical findings and results are recorded in the given form. The form is stored by researchers, and one copy is delivered to the institutional monitor during the regular meeting.

8.5 Effectiveness assessment

Follow-up surveys are performed over the long term, and the details to be recorded include surgery time, amount of blood loss, amount of blood transfusion, length of stay, early complications, late complications, recurrence and death. These surveys are standardized beforehand, and performed by all institutions in the same method and interval.

1) Factors affecting QOL

The factors affecting QOL after surgery were the scope of gastrectomy, cancer stage and anticancer drug administration. The factors affecting recovery after surgery were the insertion of nanogastric tubes, surgery time and dissection of lymph nodes. Gastrectomy for both groups was in the form of subtotal gastrectomy. Most patients had been diagnosed with gastric cancer, and only a few with advanced gastric cancer. These factors were considered as having little influence on QOL. The same anticancer drugs will be administered to patients in stage 2 or worse to minimize error. The insertion of nanogastric tubes has been associated with severe throat pain and slow restoration of gastrointestinal function. Nanogastric tubes were not inserted based on reports of successful gas removal during surgery without such insertion.

2) Post-surgery pain

- PCA (Patient-Controlled Analgesia) administration: To reduce pain adjustment differences arising from the type of PCA administration, intravenous administration was adopted for the research. Subjects were trained to self-administer analgesics whenever they experienced any post-surgery pain, and the amount administered was recorded 24 and 48 hours after surgery. - Administration of non-opioid analgesics: If

PCA is insufficient, non-opioid analgesics are administered via intramuscular injection, and the amount administered is recorded daily.

- VAS (Visual Analog Scale) : VAS is widely used in research and clinical trials as it is an effective, non-invasive pain assessment scale. Under VAS, patients rate their pain intensity on a scale of 1 to 10. Pain was recorded at rest (VAS-R) and during motion (VAS-M) for one day, two days, three days, five days and seven days following surgery.

3) Restoration of gastrointestinal function: The first passing of gas after surgery and soft food consumption are recorded.

4) Post-surgery length of stay: The length of stay after surgery is recorded.

5) Early postoperative morbidity :

① defined as complications that occur within thirty days after surgery.

② classified as follows:

A) wound morbidity: operation wound with seroma, hematoma, infection, dehiscence, or evisceration, etc.

B) surgical site morbidity: anastomosis bleeding or leakage, duodenal stump leakage, postoperative bleeding, afferent loop or efferent loop obstruction, etc.

C) lung morbidity: atelectasis, pleural effusion, empyema, pneumothorax, etc.

D) intestinal obstruction morbidity: no return of bowel movement until 5 days after surgery, mechanical obstruction with an air-fluid level or paralytic ileus on simple X-ray, etc.

E) urinary tract morbidity: frequency, nocturia, dysuria, increased white blood cell count on urine analysis, etc.

F) intra-abdominal abscess: the presence of septic fluid in the abdominal cavity that causes fever higher than 38°C and is proven by abdominal sonography or computed tomography (CT) scanning

G) postoperative pancreatitis: elevated serum amylase (> 150 U/L) with symptoms that are suggestive of pancreatitis such as back pain and fever

H) pancreatic fistula: drain amylase content greater than 1,000 U/L after postoperative day 3

I) intestinal fistula: presence of a bowel to bowel or bowel to cutaneous fistula tract that is confirmed by a fistulogram; 10) others: lymphorrhea, diarrhea, etc.

6) Late postoperative morbidity :

① defined as complications that occur after postoperative day 30.

② classified as follows:

A) adhesive ileus: mechanical or paralytic obstruction on CT scan accompanied by symptoms such as abdominal pain, vomiting, and no gas passing

B) anastomosis stricture: narrowing of the anastomosis that is confirmed by upper gastrointestinal series

C) reflux esophagitis: esophageal erosion to the stricture that is confirmed by endoscopy

D) malnutrition: iron deficiency anemia, megaloblastic anemia, or steatorrhea

E) dumping syndrome.

7) EORTC QLQ-C30

While various methods exist for the assessment of patients' QOL by doctors, emotional changes or social adaptation is difficult to measure, and doctors may prioritize factors considered unimportant by patients. The QLQ-C30 questionnaire developed by EORTC is an example of a patient-centered questionnaire. It includes five functional scales (physical, role, emotional, cognitive, and social functioning) and symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, loss of appetite, constipation, diarrhea), and scales for general health and QOL. Patient responses are converted to a score from 0 to 100. In principle, the questionnaire is administered one year after surgery.

8) STO22

The STO22 has five multi-item scales (dysphasia, eating restriction, pain, reflux, and anxiety) and four single items (dry mouth, body image, taste and hair loss). Patient responses are converted to a score from 0 to 100. First, multi-trait scaling analysis must be performed to check the Korean translation of STO22 against the original version. If the correlation between items and scales is greater than 0.4, scale classification can be considered appropriate.

Second, the reliability and validity of the Korean STO22 must be assessed. To assess the reliability of the Korean STO22, Cronbach's alpha is obtained using the internal consistency method. A Cronbach's alpha of 0.7 or higher is considered acceptable. To assess the validity of the Korean STO22, ANOVA test was performed on ECOG PS and STO22 items. Given the similarity of STO22 items and QLQ-C30, the correlation between similar items is also examined.

After verifying the reliability and validity of the Korean STO22, average values for laparoscopic gastrectomy and open gastrectomy can be compared and analyzed.

9) Recurrence

Regardless of survival and mortality, all details concerning recurrence must be accurately recorded. These include the date of recurrence, location, type and method of verification.

The recurrence pattern is classified into eight categories: remnant gastric, locoregional, peritoneal, hepatic and extrahepatic hematogenous, lymphatic, mixed, and other recurrences. ① Remnant gastric recurrence includes tumors in the anastomosis or gastric stump.

② Locoregional recurrence includes tumors in adjacent organs, including the gastric bed, porta hepatis, abdominal wall and the regional lymph nodes (perigastric, left gastric, common hepatic, celiac, and hepatoduodenal).

③ Peritoneal recurrence is defined as peritoneal seeding or Krukenberg's tumor.

④ Hematogenous metastasis is divided into hepatic and extrahepatic hematogenous recurrence. The latter includes recurrence in the lung, bone, brain, or other distant sites.

⑤ Lymphatic recurrence is defined as tumors in the paraaortic, inguinal, Virchow's or other distant lymph nodes, or lung lymphangitic metastasis.

⑥ The mixed pattern of recurrence includes those recurrences where the criteria for two or more of the above categories are met simultaneously

10) Death

Details such as date of death, cause of death and method of verification must be recorded. Intermediate assessment is performed based on the collected data.

For cases that cannot be tracked in follow-up surveys, researchers will attempt to contact the subjects by phone or mail.

11) Inflammatory and immune responses

CRP and IL-6 were used as markers of inflammatory response for patients in both groups. To compare immunity, measurements were taken for total lymphocyte, T-subset, B cell, NK cell count, IL-2, and TNF-α. These values were obtained before surgery, two hours after surgery, 24 hours after surgery, five days after surgery and 30 days after surgery. CRP and IL-6 are known to increase two hours after surgery. Blood samples were centrifuged at 3,000 rpm for five minutes and stored at –75°C~-80°C. After transferring samples from 1,000 patients to the laboratory, CRP and IL-5 were measured using latex-enhanced immunoturbidimetric assay and enzyme-linked immunosorbent assays (ELISA) respectively.

CRP and IL-5 levels were first recorded for the 1,000 patients immediately after registration for the study. The influence of inflammatory response on survival rates was analyzed following the analysis of 5-year survival.

12) Cost-effectiveness

At discharge, the total cost will be calculated and the two groups will be compared with regard to cost-effectiveness. We evaluated not only social cost which may be calculated by time needed to resume normal social activity but also "willingness to pay" reflecting individual patient preference for a particular procedure. Information regarding factors affect cost (length of hospital stay, complications, presence of comorbidity, etc.) will be collected.

9. Subject groups and statistical analysis

9.1 Subject groups

1) Intention to treat (ITT) group

The analysis is performed on all patients who have participated in clinical trials, with the exception of those meeting the exclusion criteria below.

A. A patient who withdrew consent after randomization or after surgery

B. A patient who has not undergone surgery after randomization (Patients assigned to open gastrectomy but chose to undergo laparoscopic surgery and vice versa are included in the analysis).

C. A patient who received surgery but not gastrectomy

D. A patient who underwent surgery other than open gastrectomy and laparoscopic gastrectomy (e.g. robot surgery)

E. A patient who underwent gastrectomy other than subtotal gastrectomy (e.g. proximal gastrectomy) (However, patients who received total gastrectomy due to unexpectedly large tumors are included in the analysis).

F. A patient with malignant tumors in another organ

2) Per-protocol (PP) group

The PP group excludes the following patients among ITT.

A. A patient who chose to receive surgery of the other group other than the randomly assigned surgery (including conversion of laparoscopic gastrectomy to open gastrectomy)

B. A patient who received combined resection or total gastrectomy instead of subtotal gastrectomy

C. A patient who died due to surgical complications

D. A patient who received combined resection of other organs

9.2 Statistical analysis methods

1) Analysis of variables for primary clinical trials

With regard to the five-year survival of laparoscopy-assisted subtotal gastrectomy and open subtotal gastrectomy, the non-inferiority of overall survival rate of laparoscopic gastrectomy is assessed (non-inferiority limit of 5% for 5-year overall survival)

2) Analysis of variables for secondary clinical trials

A. With regard to the five-year disease-free survival of laparoscopy-assisted subtotal gastrectomy and open subtotal gastrectomy, Kaplan-Meier curve analysis and log rank test are performed.

B. The frequency of surgery-related complications is analyzed using a chi-square test.

All deaths within 90 days of surgery are investigated, and chi-square test is performed to analyze the relationship between deaths and complications.

C. Quality of life

a. For EORTC-C30, analysis is divided into 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.

b. For EORTC-STO22, analysis is divided into the five multi-item scales (dysphasia, eating restriction, pain, reflux, and anxiety) and four single items (dry mouth, body image, taste and hair loss).

c. The multilevel mixed effects linear regression model is used to analyze the difference in QOL between groups.

D. Inflammatory and immune responses (total lymphocyte, T-subset, B cell, NK cell count, IL-2, TNF-α);

a. The difference in inflammatory response over time between the two groups is examined using the repeated measure design of general linear models.

b. The Cox proportional hazard model is used to analyze the difference in survival rate in relation to inflammatory response.

9.3 Analysis period and final analysis

1) Analysis period

Except in cases approved by the steering committee, the two groups will not be compared in terms of five-year overall survival, disease-free survival, and extent of recovery.

2) Intermediate analysis

Intermediate analysis is performed at one-year intervals even while clinical trials are being carried out. The results of analysis are provided to all researchers, and the possibility of early conclusion is determined. The trials are immediately halted if surgery-related deaths exceed 5%.

3) Final analysis

① Final analysis is performed for all date upon completion of the five-year follow-up of all registered patients. A final report and summary are prepared based on the analysis.

② The final report and summary are submitted to research participants and the steering committee of the Korean Laparoendoscopic Gastrointestinal Surgery Study Group (KLASS).

③ The steering committee concludes clinical trials after writing a comprehensive report based on the final report.

④ Once clinical trials are complete, all data will be under the ownership of the supervisor. Further materials may be provided in consultation with the steering committee if requested by research committees.

10. Safety measures for research subjects

- Expected side effects and risks for research subjects

Complications (heat and lung complications, bleeding, infection, anastomotic issues) related to all open gastrectomy and laparoscopic gastrectomy are the same as previously reported.

- Nondisclosure of identity

Patients' medical records will be kept confidential, and anonymity will be maintained even when results are presented.

- Abnormal reaction: All side effects occurring during the research will be recorded to derive the proportion of abnormal reactions. The incidence of abnormal reactions and confidence interval will be obtained for the test group and control group, and analysis will be performed using chi-square test.

11. Regulations on compensation for research subjects

Before conducting clinical trials, the principal investigator must check the following.

1) The principal investigator will assume responsibility and provide compensation if research subjects experience physical damage in the process of resolving abnormal reactions and treatment or hospitalization is required.

2) The principal investigator will exert all efforts to ensure no disadvantage to subjects in the clinical trials in accordance with these regulations.

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