Prospective Randomized Controlled Multicenter Study for Comparison of Long-term Outcomes between Laparoscopy-assisted and Open Distal Subtotal Gastrectomy with D2 Lymphadenectomy for Locally Advanced Gastric Cancer

(CLASS-01 Trial)

Study Protocol

Study Group
Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group

Supporting Academic Society
Chinese Gastric Cancer Association (CGCA)
Chinese Society of Laparo-Endoscopic Surgery (CSLES)
Chinese Society of Gastrointestinal Surgery

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Summary

Protocol Title	Prospective Randomized Controlled Multicenter Study for Comparison of Long-term Outcomes between Laparoscopy-assisted and Open Distal Subtotal Gastrectomy with D2 Lymphadenectomy for Locally Advanced Gastric Cancer
Protocol Version	V 1.02
PI	Guoxin Li
Research Centers	Southern Medical University; West China Hospital, Sichuan University; Beijing University Cancer Hospital; Fujian Medical University Affiliated Union Hospital; Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine; Zhongshan Hospital Affiliated to Fudan University; General Hospital of the People's Liberation Army; Harbin Medical University Cancer Hospital; The Third Affiliated Hospital of Sun Yat-sen University; Fujian Provincial Cancer Hospital; The Bethune First Hospital Jilin University; Renji Hospital, Shanghai Jiao Tong University School of Medicine; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; Tangdu Hospital, Fourth Military Medical University
Indications	Patients with locally advanced gastric adenocarcinoma in the mid and lower stomach
Research Purpose	The aim of this trial is to confirm the non-inferiority of laparoscopy-assisted distal D2 radical gastrectomy (LADG) to the open distal D2 radical gastrectomy (ODG) for the treatment of advanced gastric cancer patients (T2-4a, N0-3, M0) in terms of 3-year disease-free survival as primary endpoint.
Research Design	Multicenter, open label, randomized controlled, noninferiority study
Case Grouping	• Group A (study group): laparoscopic-assisted gastrectomy group • Group B (control group): Conventional laparotomy group
Determination of Sample Size	The sample size was calculated using nQuery Advisor 7.0(Statistical Solutions Ltd, 4500 Airport Business Park, Cork, Ireland) based on an expected incidence of 72.2% 3-year DFS rate in both groups, and the non-inferiority limit of 10% at a 2.5% of one-tailed significance level with a power of 90% and a balanced design (1:1 ratio for number of cases in both groups), the sample size required for each group was estimated at 422 cases. Assuming a maximum dropout rate for this clinical study of about 20%, the sample size was estimated at 528 cases for each group, with a total of 1056 cases required.
Number of Research Centers	14
Inclusion Criteria	• Age from over 18 to under 75 years old; • Primary gastric adenocarcinoma (including pap, tub, muc, sig, and • por) confirmed pathologically by endoscopic biopsy; • cT2-4a, N0-3, M0 at preoperative evaluation according to the

	• AJCC 7th Cancer Staging Manual; • Curative resection can be reached through distal subtotal • gastrectomy with D2 lymphadenectomy; • Performance status of 0 or 1 on ECOG (Eastern Cooperative • Oncology Group) scale; • ASA (American Society of Anesthesiology) score class I, , or III; • Written informed consent.
Exclusion Criteria	• Women during pregnancy or breast-feeding; • Severe mental disorder; • History of previous upper abdominal surgery (except laparoscopic • cholecystectomy); • History of previous gastrectomy, endoscopic mucosal resection or • endoscopic submucosal dissection; • Enlarged or bulky regional lymph node over 3 cm by preoperative • imaging; • History of other malignant disease within the past five years; • History of previous neoadjuvant chemotherapy or radiotherapy; • History of unstable angina or myocardial infarction within the past • six months; • History of cerebrovascular accident within the past six months; • History of continuous systematic administration of corticosteroids • within the past month; • Requirement of simultaneous surgery for other disease; • Emergency surgery due to complication (bleeding, obstruction or • perforation) caused by gastric cancer; • FEV1 50% of predicted value.
Withdrawal Criteria	• Patients intraoperatively/postoperatively confirmed as M1: preoperative examination revealed no evidence of distant metastasis but intraoperative exploration/postoperative pathological examination confirmed distant metastases (liver, peritoneum, pelvic metastasis, and distant lymph node metastasis, among others); the peritoneal lavage cytological examination result was positive after the operation; • Patients intraoperatively/postoperatively confirmed as T4b, or tumor invading the duodenum; • Patients ntraoperatively confirmed as unable to complete D2 lymph node dissection/R0 resection due to tumor: unable to complete R0 resection due to regional lymph node integration into a mass or surrounded with important blood vessels, which cannot

	be resected; • Patients intraoperatively confirmed as total gastrectomy to ensure a safe proximal incisional margin; Patients requiring simultaneous surgical treatment of other diseases; • Sudden severe complications during the perioperative period (intolerable surgery or anesthesia), which renders it unsuitable or unfeasible to implement the study treatment protocol as scheduled; • Patients confirmed to require emergency surgery by attending physicians condition after inclusion in this study; • Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study; • Treatment implemented is proven to violate study protocol
Intervention	Distal subtotal gastrectomy with D2 lymph node dissection will be conducted in accordance with the *Japanese Gastric Cancer Treatment Guideline* (the third edition 2010) • Group A cases: Laparoscopic-assisted distal gastrectomy with D2 lymphadenectomy • Group B cases: Conventional open distal gastrectomy with D2lymphadenectomy
Endpoints	Primary Endpoint: • 3-year disease-free survival rate Secondary Endpoints: • Morbidity and mortality • 3-year overall survival rate • 3-year recurrence pattern • Postoperative recovery course • Inflammatory and immune responses
Statistical considerations	All data analyses will be performed using the SAS statistical package (version 9.3, SAS Institute, Cary, North Carolina, USA). The noninferiority analysis for the primary endpoint of 3-year disease-free survival will be conducted by comparing 95% confidence intervals (calculated by Newcombe's method as recommended by the FDA and NCCLS) of survival rates between the test and control groups on a modified intent-to-treat (MITT) population basis. Baseline data and validity analyses will be conducted on a modified intent-to-treat (MITT) basis, and the primary endpoint will also be analyzed on a per-protocol (PP) basis, with the MITT analysis results prevailing. There were no planned interim analyses for 3-year DFS rate.Two interim analyses were planned for morbidity and mortality rates when half and all of the patients had been enrolled. The morbidity and mortality rates were calculated by dividing the number of affected patients by the total number of

	recruited patients based on the MITT principle. Normally distributed continuous variables will be presented as mean and standard deviation and compared using the t-test if normally distributed, or as median and interquartile range and compared using the Wilcoxon rank-sum test if non-normally distributed; while categorical data will be presented as number and percentages and compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. Survival data will be analyzed using the Kaplan-Meier method and log rank test. General linear model for quantitative indicators, logistic regression for qualitative indicators and Cox's proportional hazards model for survival data will be used to assess the effects of baseline, treatment, center, and treatment-by-center interactions. The numbers of loss to follow-up participants will be compared using the χ2 test. A two-sided P <0.05 will be considered statistically significant.

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1. Background

1.1 Gastric Cancer Epidemiology

Gastric cancer ranks fourth among the most common cancers and second among tumor-related deaths worldwide. Although the incidence of gastric cancer is declining in western countries, it persists at a high level in East Asia. According to reports, there are about 300,000-400,000 new cases of gastric cancer cases every year in China, and about 42% of gastric cancer patients worldwide are in China [1-3]. It should be noted that most gastric cancer patients in China are diagnosed at the locally advanced stage (80-90%), with a 5-year survival rate of only 20%-30% [4], which is quite different from the situation in Japan and South Korea, where early gastric cancer predominates (50-60%) [5]. Moreover, the ratio of distal gastric cancer in China is about 60%.

1.2 Treatment of Advanced Gastric Cancer

1.2.1 Surgical Treatment of Advanced Gastric Cancer

1.2.1.1 Scope for Distal Gastrectomy

In China, Japan, South Korea and other East Asian countries, most primary gastric carcinomas are located in the mid and lower thirds of the stomach [6]. Studies show that, as long as the proximal edge is sufficient, the long-term oncological effect of total gastrectomy is equivalent to that of distal subtotal gastrectomy. However, the quality of life for patients accepting distal subtotal gastrectomy is higher [7, 8]. Therefore, distal subtotal gastrectomy is most commonly practiced.

The *Japanese Gastric Cancer Treatment Guideline (third version)* specifies that in radical surgery for T2 or deeper invasion of tumor with expansive growth (Bormann I/II type), the proximal edge should be at least 3 cm from the tumor; while for tumor with invasive growth (Bormann III / IV type), the proximal edge should be at least 5 cm from the tumor [9].

1.2.1.2 Extent of Lymph Node Dissection for Distal Gastric Cancer

In East Asia, D2 lymph node dissection is the current standard surgical treatment for potentially curable locally advanced gastric cancer [9]. However, there remains controversy on the implementation of D2 lymph node dissection in both eastern and western countries. In 1999, the prospective randomized controlled clinical study conducted by the British Medical Research Council (MRC; 400 patients, 75.5% at an advanced stage) found that, relative to D1 dissection, D2 dissection did not significantly enhance patient survival while significantly increasing incidence and mortality of postoperative complications [10]. Similar results were obtained in the prospective multicenter randomized controlled clinical studies conducted in The Netherlands (711 patients, 73.0% at an advanced stage) [11]. However, 15-year follow-up results revealed that, compared with D1 dissection, D2 dissection significantly reduced the incidence of local recurrence and gastric cancer mortality [12], which led Federico Bozzetti to state in an ensuing report that the study provided sufficient evidence base for use of D2 lymph node dissection for patients with advanced gastric cancer [13].

As for the necessity of D2 + para-aortic lymph node dissection or not, the Japan JCOG9501 study showed that D2 + para-aortic lymph node dissection did not significantly enhance postoperative survival rate [14]. Therefore, for potentially curable locally advanced gastric cancer, use of D2 lymph node dissection has become the consensus in East Asia.

1.2.2 Postoperative Comprehensive Treatment of Advanced Gastric Cancer

1.2.2.1 Postoperative adjuvant chemotherapy

According to the *NCCN Gastric Cancer Treatment Guideline, 2011 Edition* and the *2010 Japanese Gastric Cancer Treatment Guideline (third edition),* patients with advanced gastric cancer (except T2N0) should receive 5-FU-based postoperative adjuvant chemotherapy after radical resection. In 2009, a meta-analysis by Sun P et al including 12 randomized controlled clinical studies (3809 patients in total) documented that for patients with advanced gastric cancer, postoperative adjuvant chemotherapy reduces the risk of death by 22% as compared to surgery alone, and concluded that D2 radical surgery combined with 5-FU-based chemotherapy is an effective treatment strategy [18].

Despite the aforementioned guidelines and meta-analysis, there is no standard first-line chemotherapy protocol, and 5-FU-based chemotherapy is conducted following the ECF, S-1, XELOX, and other protocols. The MAGIC study by the British MRC confirmed that perioperative chemotherapy based on the ECF protocol significantly enhanced disease-free and overall survival in resectable gastric cancer as compared with surgical treatment alone [19]. The large scale ACTS-GC clinical trial carried out in Japan by Sasako et al. documented that, for patients with locally advanced gastric cancer undergoing D2 gastric cancer dissection, postoperative S-1 single-agent chemotherapy significantly enhanced 5-year overall survival (S-1 group: 71.7%; surgery alone group: 61.1%) and relapse-free survival (S-1 group: 65.4%; surgery alone group: 53.1%) compared with surgery alone, which indicated that the S-1 single-agent chemotherapy is an effective postoperative treatment protocol for patients with advanced gastric cancer after radical resection in East Asia [20]. Research on patients with II, IIIA, and IIIB gastric cancer after D2 radical resection showed that the XELOX protocol is effective in patients with advanced gastric cancer (the 3-year disease-free survival rate was 74% in the study group, and 60% in the simple observation group). In China, Jin ML, et al revalidated the latter results showing that the XELOX protocol was associated with good safety and satisfactory efficacy in patients with advanced gastric cancer [21].

1.2.2.2 Postoperative Adjuvant Radiotherapy

The SWOG9008/INT-0116 study showed that combined postoperative chemoradiotherapy for patients with advanced gastric cancer significantly reduced tumor recurrence rate, prolonged median survival time and significantly improved relapse-free and overall survival [16]. In the latter study, more than 90% of the cases underwent D0/D1 resection, which increased the probability of residual positive lymph nodes, leading many western surgeons to consider that postoperative adjuvant radiotherapy and chemotherapy can overcome the shortcomings of no D2 lymph node dissection [17].

In contrast, in East Asian countries, standard D2 lymph node dissection not only provides good local control of the tumor but is associated with lower rates of surgical complications and mortality as compared to radiotherapy; therefore, gastric cancer patients who had undergone D2 radical dissection will not be subjected to routine postoperative radiotherapy; however, controversy remains on whether postoperative radiotherapy can improve the long-term survival of the patients after D2 radical dissection.

1.3 Treatment of Advanced Gastric Cancer by Laparoscopy-assisted Surgery

1.3.1 Technological Advances in Laparoscopy-assisted Surgery of Gastric Cancer

Laparoscopy-assisted surgery is characterized by being minimally invasive, with a small incision, less intraoperative blood loss, mild postoperative pain, minor postoperative

inflammatory reaction, rapid gastrointestinal function recovery, shorter hospital stay, and obvious cosmetic advantage, among others. Since Kitano et al first reported laparoscopy-assisted distal gastrectomy for early gastric cancer [22] in Japan in 1994, laparoscopic techniques have developed rapidly, and the surgical safety and oncological efficacy of laparoscopic–assisted radical gastrectomy in the treatment of patients with early-stage gastric cancer have been confirmed by numerous clinical studies [23-28].

1.3.2 Technical Feasibility and Safety of Laparoscopic–assisted Surgical Treatment of Advanced Gastric Cancer

The application of laparoscopic–assisted techniques in the treatment of advanced gastric cancer is limited by the fact that expansion of the dissection range in D2 dissection for advanced gastric cancer renders it more technically challenging than D1/D1+ dissection for early gastric cancer. However, with the experience accumulated by laparoscopic surgeons in recent years, laparoscopic–assisted surgery for advanced gastric cancer has been successfully carried out at many hospitals. Clinical studies also have proven that laparoscopic–assisted D2 radical surgery is technically feasible and clinically safe. In a prospective comparative study by Huscher CG et al of laparoscopic-assisted and open subtotal gastrectomy treatment of distal gastric cancer in 59 patients, 78% with advanced gastric cancer, there was no significant difference in the incidence of postoperative complications (OG: 27.6%; LAG: 26.7%) and surgical mortality rate (OG: 6.7%; LAG: 3.3%) between the two surgical approaches [32]. Similar findings have been reported in different countries [29-36].

1.3.3 Oncological Efficacy of Laparoscopic–assisted Surgical Treatment of Advanced Gastric Cancer

In recent years, large volume specialized centers have reported on the oncological efficacy of laparoscopic–assisted surgical treatment of advanced gastric cancer [31, 36-39]. The prospective controlled study by Huscher CG et al showed no significant difference in 5-year overall survival and 5-year disease-free survival between laparoscopic-assisted surgery and laparotomy (58.9% vs. 55.7%; and 57.3% vs. 54.8%, respectively) [32]. For advanced gastric cancer invading subserosa, Hur H reported similar 3-year overall survival and 3-year disease-free survival for laparoscopic –assisted surgery and laparotomy [31]. Likewise, a comparative study of laparoscopic-assisted surgery and laparotomy with median follow-up time of 36 months conducted by Shuang J et al in China revealed no significant difference in overall survival between the two groups of patients [36]. Debate however persists because of the lack of multicenter, randomized, controlled studies on long-term oncological efficacy of laparoscopic–assisted surgical treatment of advanced gastric cancer, which restricts its further promotion and application.

1.3.4 Multicenter Surgical Clinical Study of Gastric Cancer in China

Use of laparoscopic-assisted surgery for gastric cancer started much later in China, with only 8 cases performed in 2003; however, as shown in Figure 1, the number of procedures has been increasing rapidly, reaching almost 1000 in 2009. Against such a background, the Chinese LAparoscopic gastrointestinal Surgery Study group (CLASS) was established at Nanfang Hospital, Southern Medical University on February 2010. More than 30 large hospitals joined CLASS, and carried out the first multicenter, retrospective case-control study of laparoscopic-assisted versus open total gastrectomy in 2010. The preliminary analysis showed no significant differences between laparoscopic-assisted surgery and laparotomy in the rates of complications and in near-term oncological efficacy in the treatment of early and advanced gastric cancer. The advantages of the minimally invasive technique are very striking.

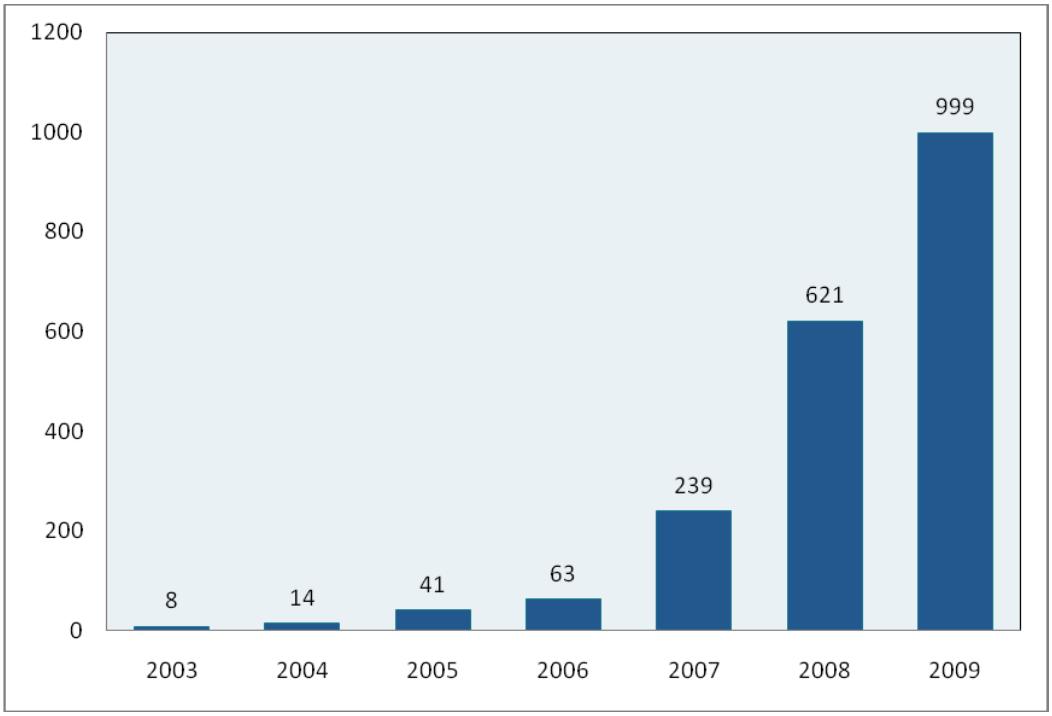

Fig. 1. Number of laparoscopic radical gastrectomy procedures for advanced gastric cancer in China (from the CLASS database)

1.4 Urgency for the study proposed

- At present, use of laparoscopic radical gastrectomy for early advanced gastric cancer is supported by high-level evidence obtained outside China; therefore, there are no data for locally advanced gastric cancer on long-term oncological efficacy of laparoscopic-assisted gastrectomy.
- The uniquely very large burden of advanced distal gastric cancer in China warrants research and resolution of controversy which affects the promotion and popularization of the minimally invasive techniques in China and restricts social and economic development.

2. Purpose

To evaluate in patients with locally advanced gastric adenocarcinoma ($T_{2\text{-}4a}$, $N_{0\text{-}3}$ and M_0) if 3-year disease-free survival as primary endpoint is noninferior for *laparoscopy*-assisted distal D2 radical gastrectomy (distal subtotal gastrectomy, D2 lymph node dissection) relative to standard treatment of open distal D2 radical gastrectomy (distal subtotal gastrectomy, D2 lymph node dissection); and to compare other long-term oncological efficacy and safety parameters as secondary endpoints.

3. Overall Design

Prospective, multicenter, open labelled, randomized controlled, noninferiority study.

3.1 Multicenter Participation

More than seven centers from Beijing, Shanghai, Guangzhou, Chengdu, Fuzhou and other cities will jointly participate in this study.

3.2 Control Group and Grouping

Group A: laparoscopic-assisted gastrectomy group (study group)

Group B: Conventional laparotomy group (control group).

3.3 Sample Size Estimate

This is a noninferiority study, with 3-year tumor-free survival rate, a class II qualitative indicator, as primary endpoint for efficacy evaluation. The reported 3-year tumor-free rate for the conventional laparotomy group is 72.2%, and it is assumed that the 3-year tumor-free rate of the study group is the same as that of the control group. After extensive discussion among the clinical experts in the project team, a noninferiority margin of 3-year tumor-free survival rate δ of 10% was chosen for this study. Using the professional sample size estimate software nQuery Advisor 7.0 (Statistical Solutions Ltd, 4500 Airport Business Park, Cork, Ireland), one-tailed statistical significance level of 0.025 and test power of 90% and balanced design (1:1 ratio of the number of cases in the study to control group), the estimated sample size required for each group was 422 cases. (References: Machin, D., Campbell, MJ Statistical Tables for the Design of Clinical Trials Blackwell Scientific Publications, Oxford (1987)). Assuming a maximum dropout rate for this clinical study of about 20%, the sample size was determined as 528 cases for each group, for a total of 1056 cases. The number of cases for each center is allocated as depicted in the table below:

3.4 Randomization

The study will use a central, dynamic, and stratified block randomization method. The control factors for randomization will be age ($\leq$60, 60 years), preoperative staging (Stages I, II, III), pathological type (signet ring cell carcinoma, non-signet ring cell carcinoma) and participating center using Pocock-Simon's minimization method. Treatment allocation with serial numbers 0001~1056 generated with SAS9.2 will be retained in the data center. After each case is enrolled, the research participating center will arrange special personnel to send through email, telephone, and SMS, among other available venues, the information of included cases (age, preoperative staging and histopathological type) to the randomization implementation department of the data center, which will determine the case grouping after analyzing the case information and will notify the study center.

3.5 Blinding Method

An open design will be used for this study.

3.6 Study Period

Case grouping cycle: the plan is to complete the inclusion of cases within 2-3 years in the 7+ centers.

Follow-up period: The inclusion of the first case is used as the starting point of the follow -up, and three years after the last case is included as the end point of follow-up.

4. Research subjects

All patients meeting all inclusion criteria and without any of the exclusion criteria are eligible for this study.

4.1 Inclusion Criteria

1) Age >18 and <75 years old;

2) The gastric primary lesion is diagnosed as gastric adenocarcinoma by endoscopic

biopsy histopathologic techniques (papillary adenocarcinoma [pap], tubular adenocarcinoma [tub], mucinous adenocarcinoma [muc], signet ring cell carcinoma [sig], and poorly differentiated adenocarcinoma [por]);

3) Preoperative clinical staging of T2-4a, N0-3, M0 (see preoperative assessment program; tumor staging is in accordance with AJCC-7th TNM);

4) It is expected that R0 surgical results will be obtained by distal subtotal gastrectomy and D2 lymph node dissection (also applies to multiple primary tumors)

5) Preoperative ECOG status score of 0/1;

6) Preoperative ASA (American society of anesthesiology) class of I –III;

7) Patients signed informed consent.

4.2 Exclusion Criteria:

1) Pregnant or lactating women;

2) Serious mental illness;

3) History of abdominal surgery (except for laparoscopic cholecystectomy);

4) History of gastric surgery (including ESD/EMR for gastric cancer);

5) Preoperative imaging examination suggests regional integration enlargement of lymph nodes (maximum diameter ≥3 cm)

6) Other malignant disease history within five (5) years;

7) Patients who received or were recommended a new adjuvant therapy;

8) History of unstable angina or myocardial infarction within six (6) months;

9) History of cerebral infarction or cerebral hemorrhage within six (6) months;

10) History of sustained systemic corticosteroid therapy within one (1) month;

11) Patients requiring simultaneous surgical treatment of other diseases;

12) Gastric cancer complications (bleeding, perforation, obstruction) requiring emergency surgery;

13) Pulmonary function test with FEV1 <50% of the expected value.

4.3 Withdrawal Criteria (excluded from PP set)

1) Cases intraoperatively/postoperatively confirmed as M1: preoperative examination revealed no evidence of distant metastasis but the intraoperative exploration/postoperative pathological examination confirmed distant metastases (liver, peritoneum, pelvic metastasis, and distant lymph node metastasis, among others); the peritoneal lavage cytological examination result was positive after the operation;

2) Cases intraoperatively/postoperatively confirmed as T4b, or tumor invading the duodenum;

3) Cases intraoperatively confirmed as unable to complete D2 lymph node dissection/R0

resection due to tumor: unable to complete R0 resection due to regional lymph node integration into a mass or surrounded with important blood vessels, which cannot be resected;

4) Cases intraoperatively confirmed as total gastrectomy to ensure a safe proximal incisional margin;

5) Cases requiring simultaneous surgical treatment of other diseases;

6) Sudden severe complications during the perioperative period (intolerable surgery or anesthesia), which renders it unsuitable or unfeasible to implement the study treatment protocol as scheduled;

7) Cases confirmed to require emergency surgery by attending physicians due to the changes in the patient's condition after inclusion in this study;

8) Patients voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study;

9) Treatment implemented is proven to violate the study protocol.

4.4 Selection of Cases

1) Patients when admitted to hospital and physical examination should meet the following conditions: age >18 and <75 years; preoperative ECOG performance score of 0/1; non-pregnant or lactating women; no serious mental illness; no history of abdominal surgery (except for laparoscopic cholecystectomy); no history of gastric surgery (including ESD/EMR for gastric cancer); no other malignant disease history within five (5) years; no history of unstable angina or myocardial infarction within six (6) months; no history of sustained systemic corticosteroid therapy within one (1) month; not requiring simultaneous surgical treatment of other diseases; pulmonary function test with FEV1 ≥50% of the expected value; and no history of cerebral infarction or cerebral hemorrhage within six months.

2) The endoscopic examination of primary lesion of patients (recommended ultrasound endoscopy EUS) and the histopathological biopsy showed gastric adenocarcinoma (papillary adenocarcinoma [pap], tubular adenocarcinoma [tub], mucinous adenocarcinoma [muc], signet ring cell carcinoma [sig], and poorly differentiated adenocarcinoma [por]).

3) Total abdominal CT did not reveal enlargement of lymph nodes in the perigastric area (maximum diameter ≥3 cm) or local invasion/distant metastasis.

4) Patient is explicitly diagnosed with gastric cancer and preoperative staging assessment of T2-4a, N0-3, M0, and is expected to undergo distal subtotal gastrectomy, D2 lymph node dissection to obtain R0 surgical results (also indicated for multiple primary cancer).

5) Patients do not require neoadjuvant chemoradiotherapy or chemotherapy and the attending doctor did not recommend them to receive the neoadjuvant chemoradiotherapy or chemotherapy.

6) Patient's ASA score is I-III.

7) Patient does not require emergency surgery.

8) At this time, the patient becomes a potentially eligible case, and then enter the **8.1 Case Inclusion Procedure.**

5. Endpoints

5.1 Primary Endpoint

- 3-year disease-free survival rate [Time Window: postoperative three years]

5.2 Secondary Endpoints

- Early complication rate and mortality rate [Time Frame: postoperative 30 days]
- 3-year overall survival rate [Time Frame: postoperative three years]
- 3-year recurrence pattern [Time Frame: postoperative three years]
- Postoperative early recovery course [Time Frame: postoperatively up to first discharge]
- Inflammatory and immune responses

6. Diagnostic Criteria for This Study

- The AJCC-7th TNM tumor staging system will be used for this study
- Diagnostic criteria and classification of gastric cancer: According to the histopathological international diagnostic criteria, it will be divided into papillary adenocarcinoma (pap), tubular adenocarcinoma (tub), mucinous adenocarcinoma (muc), signet ring cell carcinoma (sig), and poorly differentiated adenocarcinoma (por).
- Definition of advanced stage: tumor infiltration of the stomach wall reaches or exceeds the inherent muscular layer (T2); T2, T3, T4a cases will be included as study subjects while T4b cases will not.

7. Qualifications of the Responsible Surgeons that Participate in This Study

7.1 Basic principle

The responsible surgical doctors that participate in this study shall meet the following qualifications: 1. has completed at least 50 cases of traditional laparotomy and laparoscopic radical distal subtotal gastrectomy and D2 lymph node dissection surgery; and 2. has passed the video blind review of surgery.

7.2 Specific Measures

1) The medical record room of the participating units shall provide written proof of the number of past cases completed;

2) Video blind review of surgery: The applicant provides videos of open and laparoscopic radical distal subtotal gastrectomy and D2 lymph node dissection carried out during one recent month (three cases each) to the CLASS Research Council; the CLASS Research Council will randomly select the videos of two cases of open and laparoscopy-assisted surgery separately, and randomly assign three peer experts (composed of a total of 30 domestic and Japan and South Korea gastric surgery experts) to conduct blind review on the video taken. When the three review experts

unanimously approve the surgical techniques and tumor cure degree, the applicant will be permitted to participate in this study as a researcher.

8. Standard Operating Procedures (SOP)

8.1 Case Selection

8.1.1 Selection Assessment Items

Clinical examination data of patients conducted from hospital admission to enrollment into this study (time period is usually 1 week) will be considered baseline data, and must include:

1) Systemic status: ECOG score, height, weight
2) Peripheral venous blood: white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), lymphocyte count (LYM)
3) Blood biochemistry: albumin, prealbumin, total bilirubin, AST, ALT, creatinine, fasting glucose, CRP
4) Serum tumor markers: CEA, CA19-9, CA72-4
5) Full abdominal CT (slice thickness of 10mm or less, in case of allergy to the contrast agent, CT horizontal scanning is allowed only)
6) Upper gastrointestinal endoscopic ultrasonography (EUS) and biopsy, If no EUS, select ordinary upper gastrointestinal endoscopy and biopsy instead
7) Chest X-ray (AP and lateral views): cardiopulmonary conditions
8) Resting 12-lead ECG
9) Respiratory function tests: FEV1, FVC

8.1.2 Selection Application

For cases that meet all inclusion criteria and none of the exclusion criteria, prior to inclusion in this study, the research assistant of each research participating center will fill out the [Eligibility Application Form], and then fax it to the CLASS Research Committee for review to verify that they belong to eligible cases.

8.1.3 Eligibility Consultation

Contact Information and Working Hours of the CLASS Research Committee:

Address: CLASS Research Committee, Clinical Research Center, Nanfang Hospital, Southern Medical University

Tel: 020-62787171 Fax: 020-61641683

Working Hours: Monday to Friday 9:00 to 17:00 (except holidays and weekends)

Contact Information:

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E-mail: gary_mou@163.com

8.1.4 Precautions

1) Application and confirmation of eligibility should be completed preoperatively; postoperative applications will not be accepted.

2) If [Eligibility Application Form] is inadequately completed, it must be completed; otherwise, it will not be accepted.

3) After being accredited by the CLASS Research Committee, it should be archived and numbered (Baseline Number, BN) and the [eligibility confirmation notice] should be faxed to the applicant.

4) After each research participating center receives the [eligibility confirmation notice], the research assistant of each center is responsible for its custody and recording.

5) Once selected for registration, the content of the [eligibility application form] will be entered into the database; eligibility is not allowed to be artificially canceled (the relevant information cannot be deleted from the database), unless the patient declines for the information to be used in this study.

6) The data center will reject any repeatedly selected information. If this happens, the first registered data will be used (for the first time BN).

7) In the case of repeated selection or registration error, the research assistant of each

research participating center should contact the CLASS Research Committee as soon as possible for liaison, recording.

8.2 Preoperative Management

After the eligibility is obtained, surgery should be performed within one week (including the 7th day)

- For the person failing to accept surgical treatment within 1 week after selected, the reason needs be recorded in the [Pre-treatment Records].
- In case of any deterioration of the clinical conditions from the selection time to the expected day of surgery, whether to undergo an elective surgery as planned should be decided in accordance with the judgment of the doctor in charge; if an emergency surgery is required, the case should be withdrawn from PP set according to **4.3 Withdrawal Criteria**; if the doctor still performs an elective surgery, it should be registered in the [Pre-treatment Records] according to the original recording method; if the doctor cancels the surgery, is should be recorded in the [treatment end table], and the chief physician's judgment basis should be recorded in the [treatment end table] at the same time; if an elective surgery is postponed to be performed after one week, the reason should be recorded in the [Pre-treatment Records].
- For patients with nutritional risks, preoperative enteral/parenteral nutritional support is allowed.
- For elderly, smokers high-risk patients with diabetes, obesity and chronic cardiovascular/cerebrovascular or thromboembolic past history, among others, perioperative low-molecular-weight heparin prophylaxis, lower-limb antithrombotic massage, active lower limb massage, training in respiratory function and other preventive measures are recommended. For other potentially high-risk complications not specified in this study protocol, the doctor in charge of each research participating center can decide on the most appropriate approach according to clinical practice and specific needs of each center and should record it in the CRF.
- For the operative approach of the surgeries in this study, namely distal subtotal gastrectomy, D2 Lymphadenectomy, should be performed at each research center according to the Japanese *Gastric Cancer Treatment Guidelines. Physician Edition, 3rd Edition, 2010.10*. The digestive tract reconstruction method, Billroth I/Billroth II/Roux-en-Y method, should be selected by the doctor in charge according to his/her experience and the specific intraoperative circumstances.
- Preoperative fasting and water deprivation and other before-anesthesia requirements on patients should follow the conventional anesthesia program of each research participating center, which is not specified in this study.
- For prophylactic antibiotics, the first intravenous infusion should begin 30 minutes prior to surgery. It is recommended to select a second generation cephalosporin (there are no provisions on specific brands in this study); the preparation, concentration and infusion rate should comply with routine practice; and prophylaxis should not exceed postoperative three days at a frequency of one infusion every 12 hours. If patient is allergic to cephalosporins (including history of allergy or allergy after cephalosporin administration), other types of antibiotics are allowed according to the specific clinical situation and when used over the same time period mentioned.
- Patient data to be collected during the preoperative period also includes: serum immunological parameters (interleukin [IL]-6, T lymphocyte absolute count, cluster designation [CD]4 cell absolute

count, CD8 cell absolute count, natural killer [NK] cell absolute count, B lymphocyte absolute count, tumor necrosis factor [TNF]-α and CD4/CD8 ratio).

8.3 Randomization

- The study will use a central, dynamic, and stratified block randomization method. The control factors for randomization will be age (≤60, 60 years), preoperative staging (Stages I, II, III), pathological type (signet ring cell carcinoma, non-signet ring cell carcinoma) and participating center using Pocock-Simon's minimization method.
- Upon receipt by research participating centers of an [eligibility confirmation notice], the designated person is responsible for immediately sending the selected patient information (age, preoperative staging and histopathological type) to the randomized enforcement department of the data center.
- The central randomization department will determine the enrollment of cases after analyzing the case information, and will immediately inform the research center.
- The research assistant of each research participating center should receive in a timely manner the enrollment notice and will assign the patient to Group A or Group B in strict accordance with grouping assignment received.

8.4 Standardization of Surgical Practice

8.4.1 Handling Practices Followed by Both Groups

8.4.1.1 Anesthesia

The operation is to be carried out with endotracheal intubation under general anesthesia; whether epidural assisted anesthesia is applied or not is left at the discretion of the anesthetist and is not specified in this study protocol.

8.4.1.2 Acquisition of Peritoneal Lavage Cytological Specimens

Peritoneal lavage cytological specimens will be obtained upon first accessing the abdominal cavity (detailed procedure: draw ascites (if any) after laparotomy; if there is no ascites, slowly inject 100 ml physiological saline into the abdominal cavity; collect and sample the douche at the pouch of Douglas for examination).

8.4.1.3 Intraoperative Exploration

Explore the abdominal cavity for any hepatic, peritoneal, mesenteric, or pelvic metastases and gastric serosal invasion after acquisition of peritoneal lavage cytological specimens.

8.4.1.4 Regulations on Gastrectomy

The distal subtotal gastrectomy may be performed if the following oncological principles first can be satisfied:

- Follow the *Japanese Gastric Cancer Treatment Guideline (third edition for physician, Oct. 2010)* to perform distal subtotal gastrectomy (more than 2/3 of stomach will be excised)

- Requirements for gastric incisional margin: the proximal incisional margin should be at least 50 mm from the focus edge ensuring that the incisional margin is free from any cancer invasion within a radius of 10 mm and that the distal incisional margin is located at the duodenal ampulla.

8.4.1.5 Regulations on the Extent of Lymph Node Dissection

- Follow the *Japanese Gastric Cancer Treatment Guidelines (third edition for physician, Oct. 2010)* to perform the D2 lymph node dissection.
- Extent of lymph node dissection: 1,3,4sb,4d,5,6,7,8a,9,11p,12a
- The names of relevant blood vessels are as shown in the following table; the ligation positions are as shown in Figures 2 to 6.

Target Lymph Nodes for Distal Subtotal Gastrectomy and D2 Lymph Node Dissection	
1. Cut the gastrocolic and splenogastric ligaments; cut the left gastroepiploic artery; disassociate greater gastric curvature to pre-incisional margin	4sb
2. Cut the right gastroepiploic vessels	6, 4d
3. Dissect the half inner flank below the proper hepatic artery and expose the portal vein	12a
4. Cut the right gastroepiploic artery	5
5. Dissect the front and top of the common hepatic artery	8a
6. Amputate the left gastric vessels	7
7. Dissect the celiac arterial trunk	9
8. Dissect the proximal splenic artery	11p
9. Cut the right hepatogastric ligament of cardia; disassociate lesser gastric curvature to pre-incisional margin	1, 3

8.4.1.6 Regulations on Greater Omentum Resection

This study protocol requires performance of total greater omentum resection.

8.4.1.7 Regulations on Omental Bursa Resection

This study protocol requires performance of right half omental bursa resection. Whether total omental bursa resection is to be performed or not is not specified in this study protocol.

8.4.1.8 Regulations on Digestive Tract Reconstruction

The digestive tract reconstruction method is to be determined by the surgeon according to his/her own experience and the intraoperative situation, which may be any of such anastomoses as Billroth-I, Billroth-II and Roux-en-Y. If instrumental anastomosis is used, whether the manual reinforced stitching is to be performed or not on anastomotic stoma is determined by the surgeon and not specified in this study protocol.

8.4.1.9 Regulations on Surgery-related Equipment and Instruments

Energy equipment, vascular ligation method, digestive tract cutting closure, and digestive tract reconstruction instruments are determined by the surgeon in charge of the operation according to his/her own experience and actual needs and are not specified in this study protocol.

8.4.1.10 Regulations on Gastric Canal and Peritoneal Drainage Tube

Whether an indwelling gastric canal or peritoneal drainage tube is left or not after operation is determined by the surgeon in charge of the research participating center according to his/her own experience and actual needs and are not specified in this study protocol.

8.4.1.11 Regulations on Performance of Other Concurrent Operations

If any other system/organ disease is found during surgery, the responsible surgeon and the consultants of relevant departments should jointly determine performance of a concurrent operation if there is such necessity. The priority of operations is determined according to clinical routine; the patients meeting **4.3 Exclusion Criteria** will be excluded from the PP Set.

8.4.1.12 Regulations on Handling of Excluded Patients as Identified Intraoperatively

If the surgeon in charge judges and determines that the patient undergoing surgery belongs to the exclusion case group, then the research approach is suspended and the surgeon will follow routine clinical practice of the research participating center to decide subsequent treatment (therapeutic decisions as to whether to excise gastric primary focus and metastases are made by the surgeon in charge); whether to proceed with laparoscopic surgery or convert it to laparotomy will be determined by the surgeon in charge; such subsequent treatments are not specified in this study protocol.

8.4.1.13 Regulations on Imagery/Photographing

A digital camera (8 million pixels at least) will be used to take pictures which shall contain the following contents (see the example below):

(1) lymph node dissection field (5 pics):

- Inferior pylorus region (1 pic), necessarily including the right gastroepiploic arteriovenous cut position;
- Left gastroepiploic vessel cut position (1 pic), necessarily including the left gastroepiploic arteriovenous cut position;
- Right-sided area of the superior margin of pancreas (1 pic), necessarily including the front top of the entire common hepatic artery, the half front of the inferior proper hepatic artery and the cut position of right gastric artery;
- Left-sided region of the superior margin of the pancreas (1 pic), necessarily including the left gastric

arteriovenous cut position, celiac arterial trunk and proximal splenic artery;

- Right side of cardia and residual lesser gastric curvature side (1 pic).

2) After skin incision is closed (1 pic, measuring scale serving as reference object)
3) Postoperative fresh specimens (4 pics, measuring scale serving as reference object); 1 pic before and 3 pics after dissection (mark focus size; 1 pic of distal and proximal incisional margins respectively). After the specimen is cut open along the greater gastric curvature, a measuring scale is placed as reference object before taking pictures to record the following items: the distance between the tumor edge and the proximal incisional margin (1 pic), the distance between the tumor edge and the distal incisional margin (1 pic), and the focus size and appearance of the mucosal face after the specimen is unfolded (1 pic).

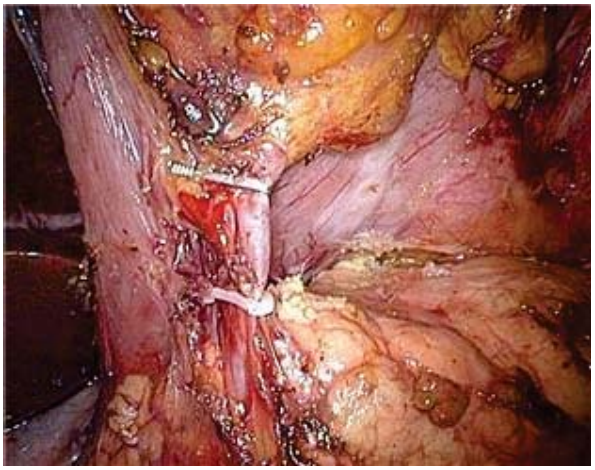

Fig. 2.Inferior pylorus area (the 6th group of lymph nodes)

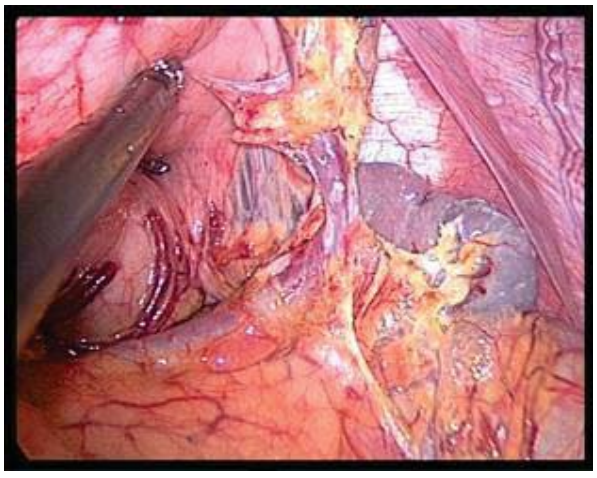

Fig. 3.Amputation position of left gastroepiploic vessels (the 4sb-th group of lymph nodes)

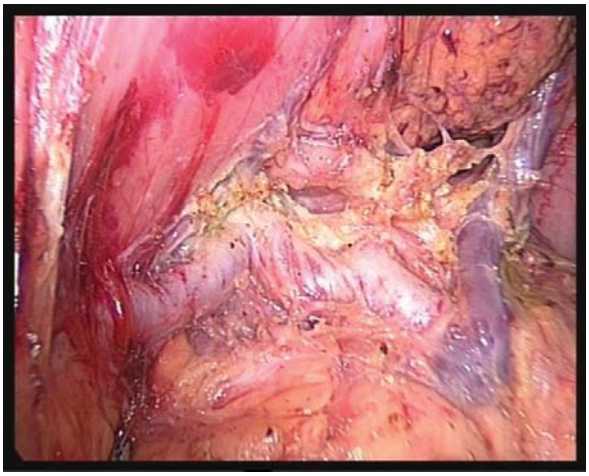

Fig. 4. Right-sided area of the superior margin of the pancreas (the 5th, 8a-th and 12a-th groups of lymph nodes)

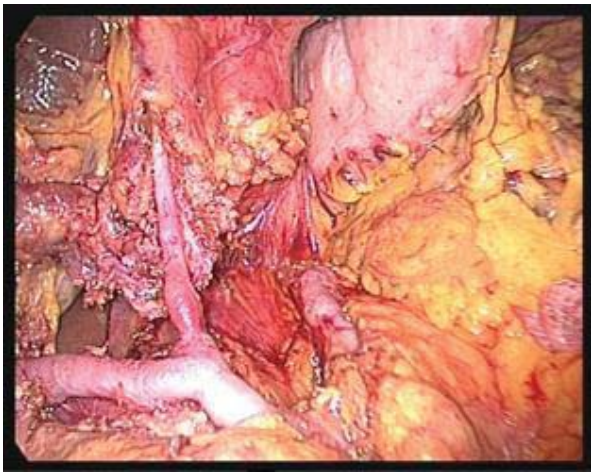

Fig. 5.Left-sided area of the superior margin of the pancreas (the 7th, 9th and 11p-th groups of lymph nodes)

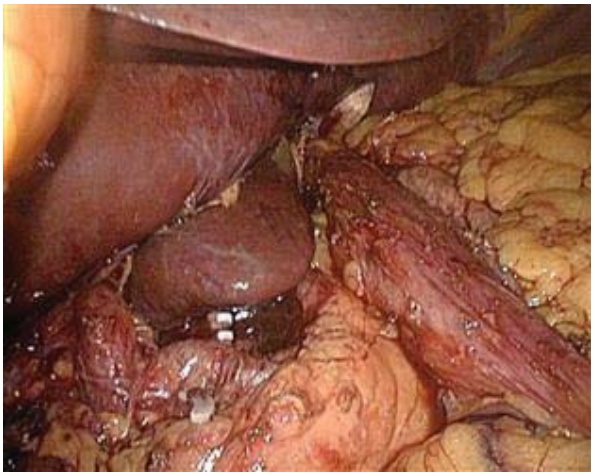

Fig. 6.Right side of cardia, and lesser curvature side of gastric remnant (the 1st and 3rd groups of lymph nodes)

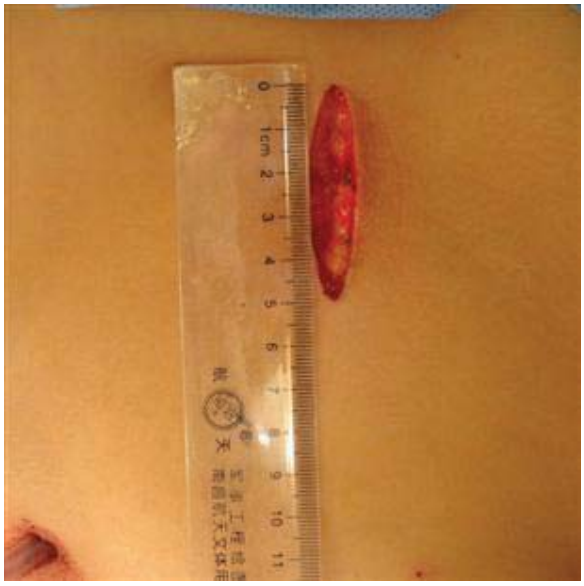

Fig. 7.Incision appearance (mark the incision length)

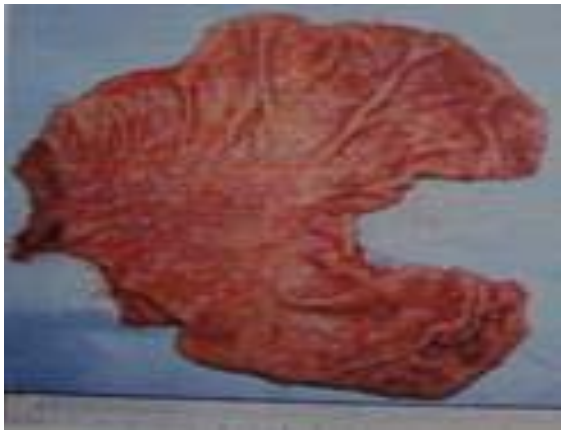

Fig.8.Specimen observation (the dissection is made along the greater gastric curvature and the observation is given to focus and incisional margin on the mucosal face; if the tumor is located at the greater gastric curvature, then the dissection is made along the lesser curvature)

8.4.1.14 Regulations on the Photo/ Image Privacy Protection and Naming

- No image data shall disclose the personal information of patients.
  - When the photos/images are viewed or reviewed, the personal information must be processed with mosaics or be covered.
  - The photographed parts should be marked with unified Chinese name: Inferior pylorus area; left gastroepiploic vessel cut position; right-sided area of superior margin of the pancreas; left-sided area of superior margin of pancreas; right side of cardia and residual lesser gastric curvature side, incision and specimens observation (indicates the picture captions).

For example:

Photo Name: [Lap-subject's random number, Inferior pylorus area]/[Open-subject's random number, Inferior pylorus area]
Folder name: [Lap-subject's random number] / [Open-subject's random number]

8.4.1.15 Criteria for Confirming Operation Quality

- To confirm the appropriateness of the surgical procedure, D2 lymph node dissection surgery quality, (auxiliary) incision length and specimen integrity will be assessed in the photographs saved (as stated above). The whole laparoscopic surgery procedure will be videotaped and the unclipped image files will be saved.
- The CLASS Research Committee will conduct review and monitoring of the surgical quality as mentioned above.

8.4.1.16 Saving of Imaging Data

- All photographs and data will be saved in the hard disk or portable digital carrier in digital form, and within one week after the operation, they should be submitted to CLASS data center for unified saving. All research participating units can back up one copy; the research participating units shall keep the laparoscopic surgery video for future inspection.
- If failure to provide the complete photo according to "Regulations on imagery/photographing" is confirmed, the CLASS Research Committee will judge and record the surgery quality as unqualified; however, the case will remain in the PP set data of this study.

8.4.2 Regulations on Laparoscopy

- The laparoscopic surgery will be conducted according to **8.4.1 Handling Principles Followed by Both Groups**
- The brands of laparoscopic system, pneumoperitoneum support system, energy equipment, clip and image storage devices are not specified in this study.

8.4.2.1 Regulations on Pneumoperitoneum

Carbon dioxide pneumoperitoneum will be used to maintain the pressure at 12-13 mmHg.

8.4.2.2 Regulations on Punctures and Auxiliary Incision

- The positions of punctures and auxiliary small incision are not specified; the number of punctures should not exceed 5.
- There should be only one auxiliary small incision whose length shall not exceed the maximum tumor diameter and necessarily will be less than 10 cm in normal cases.
- If the auxiliary small incision needs to be longer than 10 cm, the surgeon in charge should make a decision and record the reasons in the CRF.

8.4.2.3 Definition of Laparoscopic Approach

- The operations within the abdominal cavity must be performed using laparoscopic instruments with the support of a camera system.
- Perigastric disassociation, greater omentum excision, omental bursa excision, lymph node dissection, and blood vessel handling are completed under laparoscopic guidance.
- For gastrectomy and digestive tract reconstruction use of auxiliary small incisions is allowed and can be completed with an opened abdomen.

8.4.2.4 Regulations on Conversion to Laparotomy

- When intra-abdominal hemorrhage, organ damage and other serious/life-threatening complications which are difficult to control occur during laparoscopic surgery, it is necessary to actively convert to laparotomy.
- If the anesthesiologist and surgeon consider that intraoperative complications caused by carbon dioxide pneumoperitoneum may threaten the patient's life, it is necessary to actively convert to laparotomy.
- The surgeon in charge can decide to convert to laparotomy driven by other technical or equipment reasons, and will record said reasons.
- The incision length for the conversion to laparotomy is not regulated in this study.
- The cases of conversion to laparotomy still will be regarded as laparoscopic group cases and analyzed in the PP set according to the ITT (intent to treat) principle.
- The reasons for the conversion to laparotomy must be clearly recorded in the CRF.

When the auxiliary incision length is greater than 10 cm, it is defined as a case of conversion to laparotomy in this study.

8.4.2.5 Subsequent Treatment of Excluded Patients from the Laparoscopy Group

Whether the excluded patients continue to undergo surgery under laparoscopy or case is converted to laparotomy is at surgeon's discretion according to clinical experience.

8.4.3 Conventional open surgery

Laparotomy will be performed according to **8.4.1 Handling Principles Followed by Both Groups**

8.4.4 Observation Items during Surgery (same for both groups)

The research assistant should fill in appropriate content on the day of surgery. The specific items include:

1) Name of surgeon in charge
2) Operation duration (min)

3) Operation type, extent of lymph node dissection, reconstruction method

4) Incision length (cm), number of punctures

5) Whether the operation is switched to laparotomy and reasons (the laparoscopy group)

6) Intraoperative estimated blood loss (ml; from skin cutting to stitching)

7) Blood transfusion (ml): in this study, the blood transfusion event is defined as transfusion of red cell suspension (ml) or whole blood (ml)

8) Tumor position (L/M, the positions of the main body are recorded based on whether the tumor is trans-regional; in the greater/lesser curvature side, anterior/posterior wall, encirclement or not)

9) Tumor size (maximum diameter, in mm)

10) Gastric wall invasion depth, total number of dissected lymph nodes, dissected number of each group of lymph nodes, distant metastasis (position)

11) Proximal incisional margin length (mm), distal incisional margin length (mm), radical degree of operation (R0/R1/R2)

12) Intraoperative complications (i.e., occurring during the time period from skin cutting to skin stitching completion), including:

- Surgery-related complications: intraoperative injury (important organs and structures including additional blood loss caused by prominent vascular loss)
- Pneumoperitoneum-related complications: hypercapnia, mediastinal emphysema, subcutaneous emphysema, aeroembolism, and respiratory and circulatory instability caused by pneumoperitoneal pressure

13) Intraoperative death (occurring during the time period from skin cutting to skin stitching completion) regardless of reason.

8.5 Postoperative Management (same for both groups)

8.5.1 Preventive Use of Analgesics

Continuous postoperative prophylactic intravenous analgesia is allowable but not mandatory within postoperative 48 hours; its dose, type and rate of infusion should be determined by the anesthesiologist according to clinical practices and specific patient conditions. The repeated use of prophylactic analgesics is not allowed beyond 48 hours after the end of surgery, unless it is judged necessary.

8.5.2 Fluid Replacement and Nutritional Support

- Postoperative fluid infusion (including glucose, insulin, electrolytes, vitamins, etc.) or nutritional support (enteral/parenteral) will be performed based on doctor's experience and routine clinical practices, and is not specified in this study.
- After oral feeding, it is allowable to stop or gradually reduce fluid infusion/nutritional support.

8.5.3 Postoperative Rehabilitation Management

- Management methods of incision, stomach and abdominal drainage tube: Follow regular diagnosis and treatment approaches.
- Eating recovery time, diet transition strategies: Follow regular diagnosis and treatment approaches.

8.5.4 Patient Discharge Standards

In the absence of postoperative complications, and if the patient meets “oral tolerance to semi-liquid food” and “ambulation,” the patient can be discharged, which should be recorded in the CRF.

8.5.5 Postoperative Observation Items

- Definition of “postoperative day n”: One day from 0:00 to up to 24:00. Up to 24:00 on the day of surgery is “postoperative day 0;” the next day from 0:00 to up to 24:00 is “postoperative day 1;” and so on.
- From the first postoperative day until hospital discharge, the research assistant should timely fill in the following items and specific observation items including:

8.7.1 Pathological Results:

- Original lesion tissue typing (papillary adenocarcinoma [pap], tubular adenocarcinoma [tub], mucinous adenocarcinoma [muc], signet ring cell carcinoma [sig], and poorly differentiated adenocarcinoma [por])
- Stomach wall invasion depth
- Distant metastasis, and parts (including intraperitoneal exfoliative cytology)
- Histological grading (G1/G2/G3/G4/Gx)
- Radical surgery degree (R0/R1/R2)
- Pathologic specimens’ eventually total number of lymph nodes, number of lymph nodes in each group, the number of lymph node metastasis in each group, and the total number of metastases

2) Early postoperative complications:

- “Early” time period is defined as: Postoperative 30 days or less
- Observation items for early postoperative complications, include:

Wound complications (infection, effusion, adhesions, and poor healing, among others), peritoneal effusion or abscess formation, active bleeding in the abdominal cavity, gastrointestinal active bleeding, intestinal obstruction, intestinal paralysis, anastomotic stenosis, anastomotic fistula, intestinal fistula, lymphatic fistula, pancreatic juice fistula, gastroparesis, pancreatitis, pneumonia, urinary tract infection, kidney failure, liver failure, and cardiovascular and cerebrovascular events (including thrombosis, embolism) among others.

3) Blood test items (At postoperative days 1, 3, 5):

- Peripheral blood routine assessment: WBC, Hb, PLT and LYM
- Blood biochemistry: Total bilirubin, AST, ALT, BUN, creatinine, albumin, CRP, prealbumin

- Immune parameters: IL-6, T lymphocyte absolute count, CD4 cell absolute count, CD8 cell absolute count, NK cell absolute count, B lymphocyte absolute count, TNF-α and CD4/CD8 ratio

4) Postoperative rehabilitation evaluation items:

- First time of ambulation (hours)
- First time of flatulence/defecation/borborygmus (hours)
- Time to restore full-liquid food, semi-liquid food (hours)
- Daily highest body temperature from the end of surgery to postoperative discharge (°C)
- Gastric extubation time (days), daily gastric drainage volume (ml)
- Abdominal extubation drainage time (days), daily drainage flow (ml)
- Blood transfusion volume (ml) from the end of surgery to postoperative discharge: In this study, a transfusion event is defined as infusion of the red blood cell suspension (ml) or whole blood (ml)
- Postoperative hospital stay (days): Surgery time to first discharge time

5) Distal postoperative complications:

- "Distal" time is defined as: From after postoperative 30 days to 3 postoperative years
- Observation items of distal postoperative complications, include:

Incision/puncture hernia, syndrome after gastrectomy, dumping syndrome (early and late), anastomosis stricture, and mechanical obstruction, among others.

8.6 Follow-up

8.6.1 Follow-up Period and Precautions

- Each research center will arrange to have its own team and assigned staff member responsible for follow-up to carry out the follow-up of all cases enrolled in the study. Within 2 years after the surgery, a follow-up should be carried out every 3 months; after 2 years, a follow-up should be carried out every 6 months (i.e., follow-up at postoperative 1, 3, 6, 9, 12, 15, 18, 21, 24, 30 and 36 months).
- In this study, it is recommended that follow-up assessment should be conducted at the surgical center, however, other means of follow-up will not be excluded. If follow-up takes place at another hospital, it is recommended that it be a tertiary A hospital.

The staff member responsible for follow-up should tract and record the results of each examination:

- To consolidate the results of each examination, and to assess and record postoperative survival status, and presence/absence of tumor recurrence or metastasis for all patients.
- If the patient refuses follow-up according to the above protocol, it will be recorded as lost to follow-up to at time of follow-up and will be analyzed together with the cases meeting the study criteria at the end of the study (i.e., the patient will not be withdrawn from the PP set).

8.6.2 Examination Items during Follow-up

1) Systematic physical examination:

The doctor in charge will regularly conduct a systematic physical examination at the time of each follow-up, giving particular attention to superficial lymph nodes, abdomen, and signs of metastases, among others.

2) Blood test items:

- Peripheral blood routine assessment: WBC, Hb, PLT
- Blood biochemistry: Total bilirubin, AST, ALT, BUN, creatinine, albumin, prealbumin
- Serum tumor markers: CEA, CA19-9, CA72-4

3) Imaging items:

- Whole abdomen (including cavity) CT (thickness of 10 mm or less, in case of contrast agent allergy, CT horizontal scanning is only allowable or conversion to MRI)
- Upper gastrointestinal endoscopy (histopathological biopsy, endoscopic ultrasonography when necessary)
- Chest X-ray (AP and lateral views): lung field condition
- Other means of evaluation: gastrointestinal radiography, ultrasonography of other organs, whole body bone scanning, and PET-CT, among others used at physician's discretion.

8.7 Postoperative Adjuvant Therapy

8.7.1 Indications for Postoperative Adjuvant Chemotherapy

- After the surgical treatment is completed, according to the postoperative pathologic results, R0 resection cases at Phase II or above should receive postoperative adjuvant chemotherapy according to the provisions of the protocol.
- For relapse cases after non-R0 resection or R0 resection, no provisions on the follow-up treatment protocols are specified for this study; all research participating centers will decide on their own a follow-up treatment protocol according to their clinical treatment practices.

8.7.2 Postoperative Adjuvant Chemotherapy Program

- In this study, 5-FU-based combination chemotherapy will be used with recommendation to follow the XELOX protocol.
- The cycle adjuvant chemotherapy cycle will be six months (postoperative six months).
- Based on good physical strength and tolerance by patients, the first chemotherapy should begin within 8 weeks after surgery, and then a chemotherapy cycle should follow regularly.
- The presence or absence of tumor recurrence should be assessed in accordance with the follow-up plan during the chemotherapy period.
- If tumor relapse occurs during the chemotherapy, the adjuvant chemotherapy program of this study should be ceased and each research participating center should self-determine the follow-up treatment according to clinical practices, and no provisions are specified in this study. The reasons and follow-up treatment programs should be recorded in the CRF.
- If there is no tumor relapse during the chemotherapy period, adjuvant chemotherapy should be completed in the six-month period. The patient should be continued to be assessed for tumor

relapse according to the follow-up plan.

- A written consent should be obtained from the patient for adjuvant chemotherapy.
- Cases in which patients refuse postoperative adjuvant chemotherapy or to complete the full course of adjuvant chemotherapy will not be considered as withdrawal cases in this study but should be marked in the CRF and reasons should be recorded.
- For elderly patients (aged 70 or older), taking into account physical differences and to ensure patient safety, each research participating center should self-determine the chemotherapy program according to clinical practices. In this study, no particular chemotherapy recommendations or requirements are specified for elderly patients.
- Patients on adjuvant chemotherapy or irregular chemotherapy, or on a non-first-line medication will not be excluded in this study; however, the CLASS efficacy and safety evaluation committee must monitor patient safety during the follow-up period. The patient's chemotherapy medication must be recorded in the CRF.
- Method of administration of adjuvant chemotherapy, toxic reaction, and intolerance dose adjustment principles should follow the published guidelines on drug toxicity and dose adjustment for each chemotherapy program, and are not specified in this study.

8.7.3 Safety Evaluation Indicators of Postoperative Adjuvant Chemotherapy

The safety evaluation indicators for the patients enrolled in the study should be immediately filled out by the investigators before and after each postoperative adjuvant chemotherapy cycle, with specific items including:

1) Performance Status (ECOG)

2) Subjective and objective status (according to records of CTCAE v3.0 Short Name)

3) Blood tests:

- Peripheral venous blood assessment: WBC, Hb, PLT
- Blood biochemistry: albumin, Na, K, total bilirubin, AST, ALT, creatinine
- Serum tumor markers: CEA, CA19-9, CA72-4

4) Safety evaluation items to be implemented during chemotherapy when necessary (refer to CTCAE v3.0):

- Neurotoxicity
- Cardiovascular system (cardiac toxicity, ischemic heart disease, etc.)
- Bone marrow suppression and infections due to immune dysfunction
- Others

8.8 Study Calendar

Observation Stage	Systematic Physical	Blood biochemistry	Tumor markers	Electrocardiogram, respiratory function	Upper gastrointestinal endoscopy	Chest X-ray, full abdominal CT Xp	Eligibility confirmation notice	Preoperative, postoperative complications	Adverse chemotherapy events	CRF- Preoperative	CRF-Intraoperative	CRF- Postoperative	CRF- treatment end report	CRF- follow-up observation surgery
Selection Application	○	○	○	○	○	○								
After selection and prior to surgery							○			○				
Intraoperative period								○			○			
Early postoperative period								○				○	○	
Before postoperative first chemotherapy	○	○	○			○								

Regular chemotherapy		○	○	○						○					
Follow-up period Postoperative advanced stage	At postoperative 1 month	○	○	○			○		○						○
	At postoperative 3 months	○	○	○					○						○
	At postoperative 6 months	○	○	○			○		○						○
	At postoperative 9 months	○	○	○					○						○
	At postoperative 1 year	○	○	○		○	○		○						○
	At postoperative 15 months	○	○	○					○						○
	At postoperative 18 months	○	○	○			○		○						○
	At postoperative 21 months	○	○	○					○						
	At postoperative 2 years	○	○	○		○	○		○						○
	At postoperative 2 years and 6 months	○	○	○			○		○						○
	At postoperative 3 years	○	○	○		○	○		○						○

○ : Required

8.9 Definitions Involved in SOP

8.9.1 ECOG Performance Status Score

According to the simplified performance status score scale developed by the ECOG, the patients' performance status can be classified into 6 levels, namely 0-5, as follows:

- 0: Fully active, able to carry on all pre-disease performance without restriction
- 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5: Dead

Patients at Levels 3, 4 and 5 are generally considered to be unsuitable for surgical treatment or chemotherapy.

8.9.2 ASA Classification

According to the patients' physical status and surgical risk before anesthesia, the American Society of Anesthesiologists (ASA) has categorized patients into 5 levels (I-V levels) as follows:

- Class I: Well-developed patients with physical health and normal function of various organs, having a perioperative mortality rate of 0.06% -0.08%.

- Class II: Patients with mild complications and good functional compensation in addition to surgical diseases, having a perioperative mortality rate of 0.27% -0.40%.
- Class III: Patients with severe complications, restricted physical activity, but still capable of coping with day-to-day activities, having a perioperative mortality rate of 1.82% -4.30%.
- Class IV: Patients with serious complications, who have lost ability of day to day activity, often with life threatening conditions, having a perioperative mortality rate of 7.80% -23.0%.
- Class V: Moribund patients receiving a surgery or not, little chance for survival, having a perioperative mortality rate of 9.40% -50.70%.

Generally, Class I/II patients are considered good for anesthesia and surgical tolerance, with a smooth anesthesia process. Class III patients are exposed to some anesthesia risks, and therefore good preparations should be fully made before anesthesia, and effective measures should be taken to prevent potential complications during the anesthesia. Class IV patients are exposed to the most risks, even if good preoperative preparations are made, with perioperative mortality rate is being very high. Class V patients are moribund patients and should not undergo an elective surgery.

8.9.3 Oncology-related Definitions

In this study, tumor staging is based on *AJCC-7*; surgical treatment follows the *Japanese Gastric Cancer Treatment Guidelines. Physician Edition, 3rd Edition, 2010.10*, and other writing and recording principles follow the *Japanese Gastric Cancer Statute 14th*.

8.9.3.1 Primary Focus Location

The greater and lesser curvature of the stomach are divided into three equal parts, three areas of U (upper), M (middle) and L (lower), connected to the corresponding point. Esophagus and duodenum infiltration is respectively recorded as E (esophagus), and D (duodenum). If the lesions are located in two or more adjacent areas, it should be recorded in the order of the main part of the lesions.

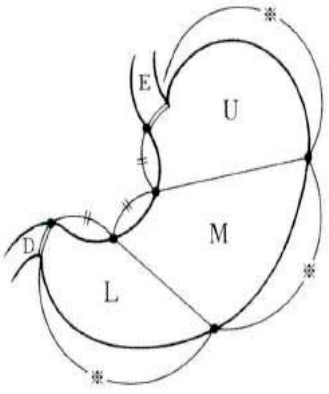

Fig. 1. Three Stomach Zones

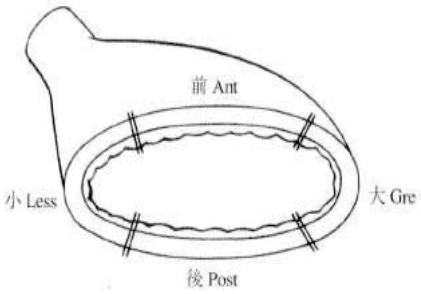

Fig. 2. Stomach Wall Sectiions

Fig. 9. Division of Three Areas of the Stomach

8.9.3.2 Tumor Staging Record

8.9.3.2.1 Recording Principle

The two staging records for clinical classification and pathological classification involve T (invasion depth), N (regional lymph node) and M (distant metastasis) which are expressed in Arabic numerals, and denoted as x if indefinite.

Clinical Classification	Pathological Classification
Physical Examination X-ray, endoscopy, diagnostic imaging Laparoscopy, intraoperative observations (Laparotomy/ Laparoscopy) Biopsy, Cytology, biochemistry, biology examination	Pathological diagnosis of the endoscopic/surgical specimens Intraperitoneal exfoliative cytology

8.9.3.2.2 Records of Tumor Invasion Depth

Tumor invasion depth is defined as follows:

- TX: unknown cancer invasion depth
- T0: No cancer found
- T1: Cancer invasion is only confined to the mucosa (M) or the submucosal tissue (SM)

  T1a: Cancer invasion is only confined to the mucosa (M)
  T1b: Cancer invasion is confined to the submucosal tissue (SM)
- T2: Cancer invasion exceeds the submucosal tissue, but is only confined to the inherent muscular layer (MP)
- T3: Cancer invasion exceeds inherent muscular layer (MP), but is only confined to the subserosal tissue (SS)
- T4: Cancer invasion involves the serosa (SE) or direct invasion of adjacent structures (SI)

  T4a: Cancer invasion involves only the serosa (SE)
  T4b: Cancer directly invades the adjacent structures (SI)

8.9.3.2.3 Records of Tumor Metastasis

1) Lymph node metastasis:

- NX: Number of lymph node metastasis is unknown
- N0: No lymph node metastasis
- N1 : Lymph node metastasis of 1-2 areas
- N2 : Lymph node metastasis of 3-6 areas
- N3: Lymph node metastasis of 7 and more areas

  N3a : Lymph node metastasis of 7-15 areas
  N3b: Lymph node metastasis of 16 and more areas

Lymph node numbers are defined as follows:

No.	Name	Definition
1	Cardia right	Lymph nodes around the gastric-wall first branch (cardia branch) of ascending branches of left gastric artery and those at cardia sides
2	Cardia left	Lymph nodes at left side of cardia and those along cardia branch of lower left diaphragmatic artery esophagus
3a	Lesser gastric curvature (along left gastric artery)	Lymph nodes at lesser curvature side along left gastric artery branch, below cardia branch
3b	Lesser gastric curvature (along right gastric artery)	Lymph nodes at lesser curvature side along right gastric artery branch, partially left side of the 1st branch in the lesser curvature direction
4sa	Left side of greater gastric curvature (short gastric artery)	Lymph nodes along short gastric artery (excluding root)
4sb	Left side of greater gastric curvature (along left gastroepiploic artery)	Lymph nodes along left gastroepiploic artery and the first branch of greater curvature (refer to the definition of No.10)
4d	Right side of greater	Lymph nodes at partially left side of the first branch in greater gastric

	gastric curvature (along right gastroepiploic artery)	curvature direction along right gastroepiploic artery
5	Superior pylorus	Lymph nodes along right gastric artery and around the first branch in lesser gastric curvature direction
6	Inferior pylorus	Lymph nodes from the root of right gastroepiploic artery to the first branch in greater gastric curvature direction, and those at the junction of right gastroepiploic veins and superior anterior pancreaticoduodenal veins (including the junction portion)
7	Left gastric artery trunk	Lymph nodes from the root of left gastric artery to the branch portion of ascending branches
8a	Anterior upper part of common hepatic artery	Lymph nodes at anterior upper part of common hepatic artery (from branch portion of splenic artery to branch portion of gastroduodenal artery)
8p	Posterior part of common hepatic artery	Lymph nodes at posterior part of common hepatic artery (from branch portion of splenic artery to branch portion of gastroduodenal artery)
9	Surrounding of celiac artery	Lymph gland that is in the surrounding of celiac artery or that is a part of each root of left artery of the stomach, common hepatic artery and splenic artery as well as that relates to celiac artery
10	Splenic hilum	Lymph gland that is in the surrounding of celiac artery and splenic hilum far away from the end of pancreas, including the first greater gastric curvature in the root of short gastric artery and left gastroepiploic artery
11p	Splenic artery proximal	Lymph gland at splenic artery proximal (in a location that divides the distance between the root of splenic artery and the end of pancreas into two equal parts, including the proximal side)
11d	Splenic artery distal	Lymph gland at splenic artery distal (in a location that divides the distance between the root of splenic artery and the end of pancreas into two equal parts, inclining to the end of pancreas)
12a	Within the hepatoduodenal ligament (along proper hepatic artery)	Lymph gland that is below a location that divides the height of confluence part of left and right hepatic ducts and bile duct in the upper margin of pancreas into two equal parts and is along proper hepatic artery (As stated in No.12a2 of regulation on bile duct carcinoma)
12b	Within the hepatoduodenal ligament (along bile duct)	Lymph gland that is below a location that divides the height of confluence part of left and right hepatic ducts and bile duct in the upper margin of pancreas into two equal parts and is along proper hepatic artery (As stated in No.12b2 of regulation on bile duct carcinoma)
12p	Within the hepatoduodenal ligament (along portal vein)	Lymph gland that is below a location that divides the height of confluence part of left and right hepatic ducts and bile duct in the upper margin of pancreas into two equal parts and is along proper hepatic artery (As stated in No.12p2 of regulation on bile duct carcinoma)
13	Back of pancreatic head	Lymph gland adjacent to the head of duodenal papilla at the back of pancreatic head (No.12b in the surrounding of the hepatoduodenal ligament)
14v	Along superior mesenteric vein	Lymph gland that is in the front of superior mesenteric vein, with inferior margin of pancreas on the upper side, right gastroepiploic vein and confluence part of superior pancreaticoduodenal vein in the right, left margin of mesenteric vein in the left and branch of middle colic vein in the lower margin.
14a	Along superior mesenteric artery	Lymph gland along superior mesenteric artery
15	Surrounding of colon middle artery	Lymph gland that is in the surrounding of colon middle artery
16a 1	Surrounding of abdominal aorta a1	Lymph gland that is in the surrounding of aorta gap (4 to 5cm wide in the surrounding of medial crus of diaphragm)
16a 2	Surrounding of abdominal aorta a2	Lymph gland that is in the surrounding of aorta from the upper margin of abdominal artery root to the lower margin of left renal vein
16b 1	Surrounding of abdominal aorta b1	Lymph gland that is in the surrounding of aorta from the lower margin of left renal vein to the upper margin of inferior mesenteric artery root
16b 2	Surrounding of abdominal aorta b2	Lymph gland that is in the surrounding of aorta from the upper margin of inferior mesenteric artery root to branch of aorta

17	Front of pancreatic head	Lymph gland that is in the front of pancreatic head, next to pancreas and under pancreatic capsule
18	Below the pancreas	Lymph gland that is the lower margin of pancreas
19	Below diaphragm	Lymph gland that is in the cavity of diaphragm and along the lower side of diaphragmatic artery
20	Hiatal part of gullet	Lymph gland that connects hiatal part of diaphragm to gullet
110	Beside the lower gullet	Lymph gland that departs from diaphragm and is next to the lower gullet
111	Above diaphragm	Lymph gland that is in the cavity of diaphragm and departs from gullet (No.20 that connects to diaphragm and gullet)
112	Posterior mediastinum	Lymph gland of posterior mediastinum departed from gullet and its hiatal part

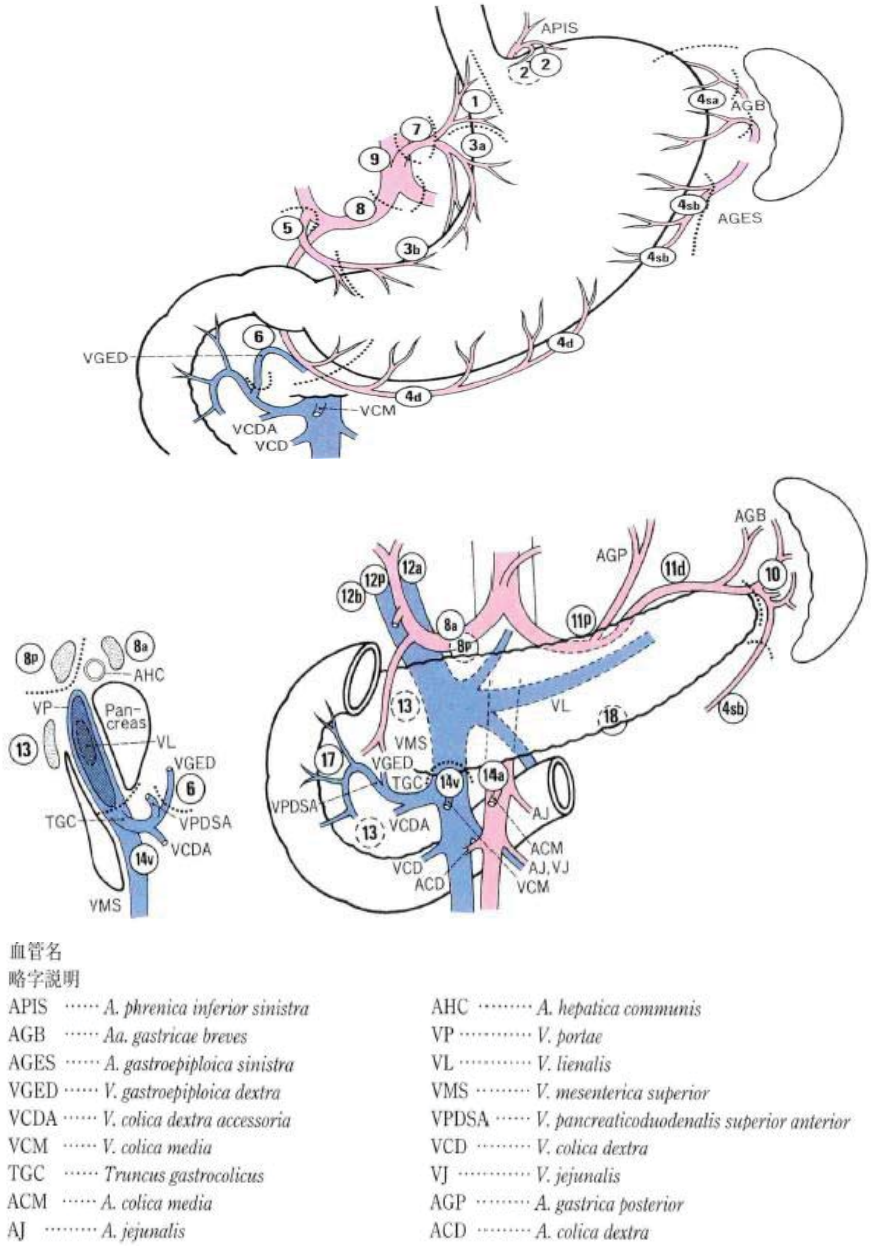

Fig. 10. Lymph node grouping

2）Distant metastasis

- M0： No distant metastasis outside of the regional lymph nodes
- M1： Distant metastasis outside of the regional lymph nodes

- MX：Presence of distant metastasis is unclear

Record the specific sites under M1 condition: peritoneum (PER), liver (HEP), lymph node (LYM), skin (SKI), lung (PUL), bone marrow (MAR), bone (OSS), pleura (PLE), brain (BRA) and meninges (MEN), intraperitoneal exfoliated cells (CY), and others (OTH).
Note: A positive examination result of intraperitoneal exfoliated cells is recorded as M1.

8.9.3.2.4 Tumor Staging

	N0	N1	N2	N3	M1
T1a,T1b	IA	IB	IIA	IIB	
T2	IB	IIA	IIB	IIIA	
T3	IIA	IIB	IIIA	IIIB	
T4a	IIB	IIIA	IIIB	IIIC	
T4b	IIIB	IIIB	IIIC	IIIC	
Any T/N	IV				

8.9.3.3 Pathologic Types and Classifications

8.9.3.3.1 Type

- Papillary adenocarcinoma
- Tubular adenocarcinoma
- Mucinous adenocarcinoma
- Signet ring cell carcinoma
- Poorly differentiated carcinoma

8.9.3.3.2 Grading

- GX classification is not possible to assess
- G1 well differentiated
- G2 moderately differentiated
- G3 poorly differentiated
- G4 undifferentiated

8.9.3.4 Evaluation of Radical Level (Degree)

8.9.3.4.1 Records of Existence or Inexistence of Cancer invasion on the Resection Stump

1) Proximal incisional margin (PM: proximal margin)

- PM (-): No cancer invasion found on the proximal incisional margin
- PM (+): Cancer invasion found on the proximal incisional margin
- PMx: Unknown cancer invasion on the proximal incisional margin

2）Distal incisional margin (DM: distal margin)

- DM (-): No cancer invasion found on the distal incisional margin
- DM (+): Cancer invasion found on the distal incisional margin
- DMx: Unknown cancer invasion on the distal incisional margin

8.9.3.4.2 Radical Records

Postoperative residual tumor, denoted with R (residual tumor): R0: curative resection; R1, R2: non-curative resection.

- RX: cannot be evaluated
- R0: no residual cancer
- R1: microscopic residual cancer (positive margins, peritoneal lavage cytology positive)

- R2: macroscopic residual cancer

9. Endpoints and Definitions for Determination of Relevant Results

9.1 Definition of Relapse and Recurrence Day

"Relapse" is considered to occur in the situations described below, and the basis of diagnosis of "Relapse" should be recorded in the CRF.

1) Determined by any imaging evaluation (X-ray, ultrasound, CT, MRI, PET-CT, endoscopy, etc.), without discrepancy among the results of several imaging examinations. When "Relapse" is diagnosed according to the results of several imaging examinations, the date of first discovery via imaging examination is defined as the "recurrence day."

2) Clinical "relapse" is diagnosed only through clinical history and physical examination without imaging or pathology diagnosis, and the date the diagnosis is made is the "recurrence day."

3) "Relapse" also could be diagnosed without imaging or clinical findings but through only cytology or tissue biopsy; the earliest cytology or tissue biopsy examination date is the "recurrence day".

4) The increase in CEA and other tumor markers alone cannot be the basis for "Relapse" diagnosis.

9.2 Endpoint Definitions

9.2.1 Disease (tumor)-free survival: DFS

- Time between the day of surgery as the starting point and the date of tumor recurrence as the end point (in case of unknown specific date of tumor recurrence, the date of death for tumor reasons is the termination time point).
- If there is no follow-up data on death or a tumor recurrence event, the final date of no relapse should be confirmed (eventually relapse-free survival confirmation date: the outpatient day or the last date to accept the inspection) as the termination point.

9.2.2 Surgical Complication Rate

- The proportion value will be calculated for the number of patients with any intraoperative/postoperative complication as the numerator and the number of all patients undergoing surgical treatment (laparoscopic surgery/laparotomy) as the denominator.
- Intraoperative/postoperative complication standards refer to early and late complications mentioned in **8.4.4 intraoperative observation items (12)** and **8.5.5 postoperative observation items (2) and (5)**

9.2.3 Mortality

- Mortality will be calculated as the ratio between the number of patients who died as numerator and number of all patients undergoing surgical treatment (laparoscopic surgery/laparotomy) as the denominator.
- Object: recorded as intraoperative death in accordance with **8.4.4 intraoperative observation items (13)**; all deaths (no matter if causally related to surgery) within 30 days after the end of surgery (including 30 days); or during a longer period of time after 31 days after end of surgery if there is conclusive evidence that there is a direct causal relationship between the patient's death and the first surgery.

9.2.4 Total Survival Time

The time between the day of surgery as a starting point and the time of death for a variety of reasons as the end point (in case of no death, the last follow-up time is considered as the termination point).

- In survival cases, the ultimate survival confirmation date is the termination point.
- In case of inability to follow-up, the last date of survival should be confirmed.

9.3 Determination of Surgical Results

9.3.1 Postoperative Rehabilitation Indicators

9.3.1.1 Time to start bowel function, to restore liquid food and semi-liquid food

- Starting from the postoperative 1 day to the first postoperative discharge, within the initial recognition of the earliest time for bowel function (flatulence/bowel movement), to restoration of fluid/semi-fluid diet; records are made hourly.
- Flatulence/bowel movement on the day of surgery is excluded.
- In case of no flatulence/bowel movement/restoration of liquid/semi-liquid diet before the first postoperative discharge, the discharge time should be recorded as the time of flatulence/bowel movement/restoration of liquid/semi-liquid diet.
- The initial time of flatulence/bowel movement/restoration of liquid/semi-liquid diet is per patient report.

9.3.1.2 Highest Body Temperature

The highest body temperature starting from postoperative day 1 up to 3 days should be measured at least three times a day.

9.3.2 Percentage of Laparoscopic Surgeries Completed

Ratio expressed as percentage for completion of laparoscopic surgeries will be calculated with number of patients failing to convert to laparotomized laparoscopic gastrectomy as the numerator, and number of all patients undergoing surgical treatment (laparoscopic surgery/laparotomy) as the denominator.

9.3.3 Ratio of Conversion to Laparotomy

- Ratio, expressed as percentage, of conversion to laparotomy treatment will be calculated with number of patients converting to laparotomy treatment from a laparoscopy surgery for any reason as the numerator and number of patients undergoing laparoscopic surgery treatment as per protocol among all patients receiving surgical treatment as the denominator.
- In this study, a laparoscopy-assisted incision of more than 10cm should be deemed as conversion to laparotomy treatment.

10. Statistical Analysis

10.1 Definition of Population Set for Statistical Analysis

1) Intent-to-treat Population (ITTP):

Cases that expressed intention to participate in the study and signed an informed consent form.

2) Modified Intent-to-treat Population (MITTP, modified intent-to-treat population):

Cases that underwent randomization and laparoscopic surgical treatment or conventional laparotomy, with records of data of at least one valid efficacy evaluation after intervention.

3) Per-protocol Population (PPP):

Cases complying with the study protocol, with good compliance and completed CRF, allowing statistical analysis of efficacy. The main analytical results are consistent with those of the MITT analysis.

4) Safety Analysis Population (SAP):

All cases that underwent randomization and laparoscopic surgical treatment or conventional laparotomy, with records of data for safety evaluation after intervention constitute a safety analysis population of this study, allowing a statistical description and analysis of safety indicators and incidence of adverse reactions.

10.2 Statistical Analysis Plan

- Statistical software: A database will be established and data will be entered into it using Epidata3.0 Statistical analyses will be performed using SAS9.2 statistical software.
- Primary endpoint analysis: The noninferiority analysis for the primary endpoint of 3-year disease-free survival will be conducted by comparing 95% confidence intervals (calculated by Newcombe's method as recommended by the FDA and NCCLS) of survival rates between the test and control groups on a modified intent-to-treat (MITT) population basis and using a noninferiority margin for 3-year tumor-free survival rate δ of 10% was chosen for this study.
- Statistical Analysis Populations: Analyses of baseline data and validity analyses will be conducted on a modified intent-to-treat (MITT) basis, and the primary endpoint will also be analyzed on a per-protocol (PP) basis, with the MITT analysis results prevailing. Safety evaluation, including laboratory test data, also will be conducted in the safety analysis population (SAP), and two interim analyses on an MITT basis will be conducted and reported for morbidity and mortality rates when half and all the projected study patient population has been enrolled.
- Descriptive Statistics for endpoints: Normally distributed continuous variables will be presented as mean and standard deviation and compared using the t-test if normally distributed, or as median and interquartile range and compared using the Wilcoxon rank-sum test if non-normally distributed; while categorical data will be presented as number and percentages and compared using the Pearson χ^2 test or the Fisher exact test, as appropriate. Survival data (time and rate) will be analyzed using the Kaplan-Meier method and log rank test. General linear model for quantitative indicators, logistic regression for qualitative indicators and Cox's proportional hazards model for survival data will be used to assess the effects of baseline, treatment, center, and treatment-by-center interactions. The numbers of loss to follow-up participants will be compared using the $\chi 2$ test. A two-sided $P < 0.05$ will be considered statistically significant.
- Attrition Analysis: Comparison of total attrition rates and attrition rates due to adverse events between the two groups will be conducted using Pearson $\chi 2$ test.
- Method for Determination of Outliers: Any observed value that is thrice lower or higher than the lowest (P25) or highest (P75) interquartile range will be considered an outlier. The effect of retention and elimination of outliers will be analyzed by sensitivity analysis; in the case of no contradiction, the data shall be retained; in the case of any contradictory, a decision shall be made on individual cases.
- Subgroup analysis: Analyses of the possible impact of particular prognostic factors on results is not excluded if possible.
- Interim analysis: As mentioned, two interim analyses on an MITT basis will be conducted and reported for morbidity and mortality rates when half and all the projected study patient population has been enrolled.

11. Data Management

11.1 Case Report Form (CRF)

11.1.1 CRF Types and Submission Deadline

CRFs used in this study and their submission deadlines are as follows:

1) Case Screening: 7 days prior to surgery (time frame of three days)
2) Enrolling: submitted to the data center at one day prior to surgery
3) Surgery: within 1 day after surgery
4) Postoperative discharge: within three days after the first discharge
5) Follow-up records: 7 days after each specified follow-up time point

11.1.2 CRF Transmittal Methods

In this study, the paper CRF and web-based ECRF form are used for information and data transmittal.

11.1.3 CRF Amendment

After the start of the study, if the CRF is found to lack items that are then deemed pertinent, under the premises of ensuring the amendment of the CRF does not cause medical and economic burden and increased risks to the selected patients, the CRF can be modified after the CLASS Research Committee adopt it through discuss at the meeting. If the amendment of the CRF requires no changes to this study protocol, the latter will not be modified. Submission of a report or application to each research participating hospital's IRB for the CRF amendment should follow the provisions of the various hospitals.

11.2 Monitoring and Supervision

- To assess whether study implementation follows protocol and data are being collected properly, monitoring should be conducted at each participating site on a monthly basis during the enrollment period and every two months during the follow-up period.
- The data center should periodically submit the monitoring reports to the Research Committee, the Research Responsible Person and Efficacy and Safety Evaluation Committee for discussion and analysis in accordance with relevant monitoring provisions. Regular monitoring is aimed at providing feedback for improving the scientific and ethical nature of the study rather than trying to expose study or hospital issues. The Research Committee, the Research Responsible Person and the person in charge of research at the participating hospital should strive to improve and to avoid the problems pointed out in the regular monitoring reports.

11.2.1 Monitoring Items

- Data Collection Completion Status: By selected registration numbers (cumulative and for each time period, overall and each hospital)
- Eligibility: Not eligible patients/potentially ineligible patients (different hospitals)
- Different end of treatment, the reasons for suspension/end (different hospitals) of the study protocol
- Background factors, pre-treatment report factors, post-treatment report factors when selected for registration
- Severe adverse events (different hospitals)
- Adverse events/adverse reactions (different hospitals)
- Laparoscopic surgery completion percentage (different hospitals)
- Proportion of conversion to laparotomy (different hospitals)
- Protocol deviation (different hospitals)
- Disease-free survival /overall survival (all patients selected for registration)
- Progress and safety of the study, other issues

11.2.2 Acceptable Range of Adverse Events

Treatment-related death and life-threatening complications caused by surgeries occur relatively rarely and partly are dependent on the qualifications of the research participating hospitals and their staff; a rate of over 3% is considered unacceptable. If treatment-related death is suspected or non-hematologic Grade 4 toxicity having a causal relationship with the surgery is determined, adverse events should be reported to the CLASS Efficacy and Safety Evaluation Committee. If the number of treatment-related deaths or the number of patients with determined non-hematologic Grade 4 toxicity having a causal relationship with the surgery reached 15, the final incidence proportion of adverse events would be expected to exceed 3%, and therefore the inclusion of patients must be immediately suspended. Whether the study can continue should be determined by the CLASS Efficacy and Safety Evaluation Committee.

11.2.3 Deviation/Violation of Study Protocol

Surgical resection, clinical examinations, or toxicity and efficacy evaluation that are not conducted in accordance with the study protocol are considered study protocol deviations. Deviations prespecified by the Data Center and Research Committee (allowed up to after the start of the study in special circumstances) that are found during monitoring to exceed acceptable ranges as specified for each study center should be included in the monitoring report under “possible cases of deviation,” and listed under the following categories after discussion with the Research Committee:

11.2.3.1 Violation

A violation is a clinically inappropriate deviation involving at least one of the following:
(1) Endpoint evaluation affecting the study
(2) Doctor in charge/hospital
(3) Intentional or systematic
(4) Poses significant risk to patient
Violation should be documented in detail.

11.2.3.2 Acceptable Deviation

- Deviation within the acceptable range set by the Research Representative/Committee and the Data Center for each item before the beginning of the study or after the beginning of the study.
- They do not need to be recorded in the monitoring report.

11.2.3.3 Deviation

- Items that do comply with **11.2.3.1** nor with **11.2.3.2** are deviation items
- Specific deviations that occur several times should be highlighted as red flags.
- When the monitoring report is discussed, the following cases should be classified:

1) deviated from undesired results: should be reduced
2) deviation (inevitable): not to be actively reduced
3) deviation (clinically appropriate): positive affirmation of the judgment of the chief physician/ hospital

12. Relevant Provisions on Adverse Events

The evaluation in this study refers to CTCAE v3.0 and “Accordion Severity Grading System”

12.1 Expected Adverse Events

12.1.1 Surgery-related Adverse Events

See the adverse events mentioned for surgical complications in **9.2 Definition of the study endpoint.**

12.1.2 Adverse Events Caused by Worsening Primary Diseases

Adverse events relating to various forms of deterioration in primary diseases should be recorded according to Short Name of CTCAEv3.0, including:

1) Adverse events caused by the deterioration of the primary lesions and peritoneal disseminated lesions:

   Gastrointestinal adverse events: loss of appetite, constipation, dehydration, abdominal fullness, heartburn, nausea, gastrointestinal occlusion-[stomach, duodenum, ileum, colon, small intestine - cannot be broken down], gastrointestinal perforation-[stomach, duodenum, jejunum, ileum, colon], digestive tract stenosis-[stomach, duodenum, jejunum, ileum, colon], vomiting, hyponatremia, gastrointestinal bleeding-[stomach, duodenum, jejunum, ileum, colon]
2) Adverse events caused by deterioration of liver metastases:

Abnormal metabolism/laboratory test values: AST, ALT, bilirubin, alkaline phosphatase

3) Adverse events caused by deterioration of lung metastases:

Lung/Upper Respiratory Tract: atelectasis, dyspnea, hypoxemia, airway occlusion-[bronchial]

4) Adverse events caused by deterioration of other focus metastases:

Pain: pain-[metastasis sites], hypercalcemia

5) Adverse events caused by deterioration of systemic status:

- Systemic status: fatigue, weight loss, cachexia quality
- Blood /bone marrow: hemoglobin, platelet
- Cardiovascular system: hypotension
- Lymphatic system: edema: head and neck, limbs, trunk/ genitalia, viscera
- Metabolic/clinical laboratory values: low albumin, AST, ALT, acidosis, creatinine, hyperglycemia, hypoglycemia, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, other electrolyte disturbances
- Lung/Upper Respiratory Tract: pleural effusion (non-malignant), dyspnea, hypoxemia, pulmonary infections
- Renal/genitourinary system: cystitis, renal failure, oliguria/anuria

12.2 Evaluation of Adverse Events

- Evaluation of adverse event/adverse reaction are based on [Accordion Severity Grading System] and [CTCAE v3.0]; for more comprehensive detail, refer to the latter sources.
- Adverse events will be graded 0 ~ 4 as per definition. For treatment-related death, fatal adverse events are classified as Grade 5 in the original CTCAE.
- Toxicity items specified in the [surgery-related adverse events], Grade and the discovery date of Grade should be recorded in the treatment process report. For other toxicity items observed, observed Grade 3 toxicity items are only recorded in the freedom registration column of the treatment process report, as well as Grade and the discovery date of Grade. Grade recorded in the treatment process report must be recorded in the case report form.
- CTCAE v3.0, the so-called “Adverse Event”, “all observed, unexpected bad signs, symptoms and diseases (abnormal value of clinical examination are also included) in the treatment or disposal, regardless of a causal relationship with the treatment or handling, including determining whether there is a causal relationship or not”.
- Therefore, even if events were “obviously caused by primary disease (cancer)” or caused by supportive therapy or combination therapy rather than the study regimen treatment (protocol treatment), they are “adverse events”.
- For adverse event data collection strategy, the following principles should be complied with in this study:

1) Adverse events within 30 days from the last treatment day of the study regimen treatment (protocol treatment), regardless of the presence or absence of a causal relationship should be completely collected. (When adverse events are reported, the causality and classification of adverse events are separately discussed)

2) For adverse events within 31 days from the last treatment day of the study regimen treatment (protocol treatment), only those determined (adverse reactions, adverse drug reactions) to have a causal relationship (any of definite, probable, possible) with the protocol treatment will be collected.

12.3 Reporting of Adverse Events

- When “severe adverse events” or “unexpected adverse events” occur, the Research Responsible Person of each research participating unit should report them to the CLASS Research Committee/PI (Li Guoxin). The CLASS Research Committee should send the report style to each research participating unit before the study is started.
- Based on the relevant laws and regulations, adverse events should be reported to the province (city) Health Department at the location of each research center. Severe adverse events based on clinical research-related ethical guideline should be reported to the person in overall charge of the medical institution. The appropriate reporting procedures should be completed in accordance with the relevant provisions of all medical institutions at the same time. The person in charge of research of each research participating unit should hold accountability and responsibility for the emergency treatment of patients with any degree of adverse events to ensure patient safety.

12.3.1 Adverse Events with Reporting Obligations

12.3.1.1 Adverse Events with Emergency Reporting Obligations

Any of the following adverse events should be reported on an emergent basis:

- All patients who die during the course of treatment or within 30 days from the last treatment day, regardless of the presence or absence of a causal relationship with the study regimen treatment. Also, cases of discontinuation of treatment, even if within 30 days from the last treatment day, those patients are also emergent reporting objects. (“30 days” refers to day 0, the final treatment day, 30 days starting from the next day)
- Those patients with unexpected Grade 4 non-hematologic toxicity (CTCAE v3.0 adverse events other than the blood/bone marrow group), having a causality of treatment (any of definite, probable, possible) who are emergent reporting objects.

12.3.1.2 Adverse Events with Regular Reporting Obligations

One of the following adverse events are regular reporting objects:

1) After 31 days from the last treatment day, deaths for which a causal relationship with treatment cannot be denied, including suspected treatment-related death; death due to obvious primary disease is included.
2) Expected Grade 4 non-hematologic toxicity (CTCAE v3.0 adverse events other than the blood/bone marrow group).
3) Unexpected Grade 3adverse events: Grade 3 adverse events are not recorded in the **12.1 expected adverse events**.
4) other significant medical events: adverse events that the study group deems cause important and potentially permanent, significant impact on their offspring (MDS myelodysplastic syndrome, except for secondary cancer)

Adverse events among above (2)-(4), determined to have a causal relationship (any of definite, probable, possible) with the study regimen are regular reporting objects.

12.3.2 Reporting Procedure

12.3.2.1 Emergency Reporting

- In case of any adverse event on emergency study reporting objects, the doctor in charge will quickly report it to the Research Responsible Person of the research participating hospitals. When the Research Responsible Person of the hospital cannot be contacted, the coordinator or the doctor in charge of the hospital must assume the responsibility on behalf of the Research Responsible Person of the hospital.

- First Reporting: Within 72 hours after the occurrence of adverse events, the Research Responsible Person of the hospital should complete the “AE/AR/ADR first emergency report” and send it to the CLASS Research Committee by FAX and telephone.
- Second Reporting: The Research Responsible Person of each research participating hospital completes the “AE/AR/ADR Report” and a more detailed case information report (A4 format), and then faxes the two reports to the CLASS Research Committee within 15 days after the occurrence of adverse events. If any autopsy examination, the autopsy result report should be submitted to the CLASS Research Committee.

12.3.2.2 General Reports

The Research Responsible Person of each research participating hospital completes the “AE/AR/ADR report”, and then faxes it to the CLASS Research Committee within 15 days after the occurrence of adverse events.

12.4 Responsibilities and Obligations of Research Responsible Person/Research Committee

12.4.1 Judgment of Study Discontinuation and Necessity for Sending an Emergency Notice to the Hospital

After the receipt of the report from the Research Responsible Person of the research participating hospital, the CLASS Research Committee replies to the Research Responsible Person of the unit for confirmation and negotiation, and then they jointly determine the urgency and importance of reporting events; if necessary, they can temporarily stop the study, and contact all research participating hospitals to take emergency notification countermeasures. According to the urgency degree, the data center should contact the research participating hospitals by telephone or by fax as soon as possible after the initial contact by phone.

12.4.2 Report to CLASS Efficacy and Safety Evaluation Committee

- After the CLASS Research Committee reports adverse events in line with **11.3.1 adverse events with reporting obligations** in the emergency reports or regular reports to the Research Responsible Person of research participating units, and discusses and clarifies the adverse events, the CLASS Research Committee should submit a report in writing to the Efficacy and Safety Evaluation Committee within 3 days after the occurrence of adverse events and request a review of the Research Responsible Person as to the suitability of analysis of cause of the adverse events and handling of the adverse events.
- At that time, “AE/AR/ADR First Emergency Report” and “AE/AR/ADR Report” submitted by the research participating hospital should include the discussion results and countermeasures of the CLASS Research Committee/Research Responsible Person (including judgment on research continuation/discontinuation). For death within 30 days, treatment-related death among death after 31 days and expected Grade 4 non-hematologic toxicity, not only the course of the individual patient should be included but also whether the frequency of occurrence falls within the expected range. If the frequency of occurrence falls outside the expected range, it should be faithfully recorded in the “II classification of adverse events-others” of “AE/AR/ADR Report”.

12.4.3 Notice to the Research Participating Hospitals

- After submitting the report to the CLASS Efficacy and Safety Evaluation Committee, the CLASS Research Committee/Research Responsible Person should report the review, proposal content of the CLASS Efficacy and Safety Evaluation Committee in writing to all research participating hospitals.
- If failing to submit the report to the CLASS Efficacy and Safety Evaluation Committee, the CLASS Research Committee/Research Responsible Person should report their judgment in writing to the Research Responsible Person of a research participating hospital that submitted the report.

12.4.4 Discussion of Adverse Events Under Regularly Monitoring

During regular monitoring, the CLASS Research Committee/Research Responsible Person should carefully discuss study adverse events in the monitoring report submitted by the research data center to confirm whether there is under-reporting of adverse events for each research participating hospital. Presence or absence of under-reporting adverse events should be clearly documented in the discussion results of [regularly monitoring report] of the CLASS Research Committee.

12.5 Review of CLASS Efficacy and Safety Evaluation Committee

The CLASS Efficacy and Safety Evaluation Committee reviews and discusses the report in accordance with the procedures recorded in the *Clinical Safety Information Management Guideline*, and makes recommendations in writing for the Research Responsible Person, including whether to continue to include study objects or to modify the study protocol.

13. Ethical Considerations

13.1 Responsibilities of Investigators

The investigators are responsible for the conduction of this study at their centers. The investigators will ensure the implementation of this study in accordance with the study protocol and in compliance with the *Declaration of Helsinki*, as well as domestic and international ethical guiding principles and applicable regulatory requirements. It is specially noted that, the investigators must ensure that only subjects providing informed consent can be enrolled in this study.

13.2 Information and Informed Consent of Subjects

An unconditional prerequisite for subjects to participate in this study is his/her written informed consent. The written informed consent of subjects participating in this study must be given before study-related activities are conducted.

Therefore, before obtaining informed consent, the investigators must provide sufficient information to the subjects. In order to obtain the informed consent, the investigators will provide the information page to subjects, and the information required to comply with the applicable regulatory requirements. While providing written information, the investigators will orally inform the subjects of all the relevant circumstances of this study. In this process, the information must be fully and easily understood by non-professionals, so that they can sign the informed consent form according to their own will on the basis of their full understanding of this study.

The informed consent form must be signed and dated personally by the subjects and investigators. All subjects will be asked to sign the informed consent form to prove that they agree to participate in the study. The signed informed consent form should be kept at the research center where the investigator is located and must be properly safe kept for future review at any time during audit and inspection throughout the inspection period. Before participating in the study, the subjects should provide a copy of signed and dated informed consent form.

At any time, if important new information becomes available that may be related to the consent of the subjects, the investigators will revise the information pages and any other written information which must be submitted to the IEC/IRB for review and approval. The revised information approved will be provided to each subject participating the study. The researchers will explain the changes made to the previous version of ICF to the subjects

13.3 Identity and Privacy of Subjects

After obtaining an informed consent form, each selected subject is assigned a subject number (Allocation Number). This number will represent the identity of the subject during the entire study and for the clinical research database of the study. The collected data of subjects in the study will be stored in the ID.

Throughout the entire study, several measures will be taken to minimize any breaches of personal information, including: 1) only the investigators will be able to link to the research data of the subjects to themselves through the identify table kept at the research center after authorization; 2) during onsite auditing of raw data by the supervisors of this study, as well as relevant inspection and inspection visits by the supervision departments, the personnel engaging in the above activities may view the original medical information of subjects that will be kept strictly confidential.

Collection, transmission, handling and storage of data on study subjects will comply with the data protection and privacy regulations. This information will be provided to the study subjects when their informed consent is being obtained for treatment procedures in accordance with national regulations.

13.4 Independent Ethics Committee or Institutional Review Committee

Before beginning the study, the Research Center will be responsible for submitting the study protocol and relevant documents (informed consent form, subject information page, CRF, and other documents that may be required) to the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) to obtain their favorable opinion/approval. The favorable opinions/approval documents of the IEC/IRB will be archived in the research center folders of the investigators.

Before beginning the study at the center, the investigators must obtain written proof of favorable opinions/approval by the IEC/IRB, and should provide written proof of the date of the favorable opinions/approval meeting, written proof of the members presenting at the meeting and voting members, written proof of recording the reviewed study, protocol version and Informed Consent Form version, and if possible, a copy of the minutes.

In case of major revisions to this study, the amendment of the study protocol will be submitted to the IEC/ IRB prior to performing the study. In the course of the study, the relevant safety information will be submitted to the IEC/IRB in accordance with national regulations and requirements.

13.5 Regulatory Authority

The study protocol and any relevant documents (for example, the study protocol, the subject's informed consent form) will be submitted according to the *Ethical Review Approach of Biomedical Research Involving Human Beings (Trial)* (2007) and the applicable regulatory requirements of our country or will notify the ethical review guidance counseling organization of the provincial health administrative departments at the location of each research center.

14. Organizations and Responsibilities of Study

14.1 CLASS Research Committee

- Responsible for developing study protocol, auditing eligibility for inclusion and guiding the interpretation of informed consent; also responsible for the collection of adverse event reports, guiding the clinical diagnosis and treatment of such events and the emergency intervention of serious adverse events.
- Person in Charge of CLASS Research Committee: Li Guoxin (General Surgery, Nanfang Hospital, Southern Medical University)
- Address: General Surgery, Nanfang Hospital, No.1838, North of Guangzhou Avenue, Guangzhou, Guangdong. Postcode: 510515, China; Tel:020-61641681; Fax:020-61641683; Mobile: 13802771450 ; E-mail : gzliguoxin@163.com
- Research Representative: Li Guoxin (General Surgery, Nanfang Hospital, Southern Medical University)
- Address: General Surgery, Nanfang Hospital, No.1838, North of Guangzhou Avenue, Guangzhou, Guangdong. Postcode: 510515, China; Tel:020-61641681; Fax:020-61641683; Mobile: 13802771450 ; E-mail : gzliguoxin@163.com
- Research centers assigned by the CLASS to participate in this study (hospitals listed in no

Name	Title	Unit	Location
Guoxin Li	Professor	Nanfang Hospital, Southern Medical University	Guangzhou, Guangdong
Jiankun Hu	Professor	West China Hospital, Sichuan University	Chengdu, Sichuan
Changming Huang	Professor	Fujian Medical University Affiliated Union Hospital	Fuzhou, Fujian
Ziyu Li	Professor	Beijing University Cancer Hospital	Beijing
Xiangqian Su	Professor	Beijing University Cancer Hospital	Beijing

Weiguo Hu	Professor	Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine	Shanghai
Yihong Sun	Professor	Zhongshan Hospital Affiliated to Fudan University	Shanghai
Xiaohui Du	Professor	General Hospital of the People's Liberation Army	Beijing
Yingwei Xue	Professor	Harbin Medical University Cancer Hospital	Harbin, Heilongjiang
Hongbo Wei	Professor	The Third Affiliated Hospital of Sun Yat-sen University	Guangzhou, Guangdong
Mingang Ying	Professor	Fujian Provincial Cancer Hospital	Fuzhou, Fujian
Jian Suo	Professor	The Bethune First Hospital Jilin University	Changchun,Jilin
Gang Zhao	Professor	Renji Hospital, Shanghai Jiao Tong University School of Medicine	Shanghai
Kaixiong Tao	Professor	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Wuhan, Hubei
Xianli He	Professor	Tangdu Hospital, Fourth Military Medical University	Xian, Shanxi

- particular order):

- Chief Statistical Expert of CLASS Research Committee: Chen Pingyan (Department of Biological Statistics, Southern Medical University)
- CLASS Study Committee Managing office

  Location: General Surgery, Southern Hospital (Guangzhou)
  Secretary-General: Hu Jiankun Secretary: Hu Yanfeng
  Address: General Surgery, Nanfang Hospital, No.1838, North of Guangzhou Avenue, Guangzhou, Guangdong, Post Code: 510515
  Tel 020 -62787170/020-62787171 Mobile: 13632494551 (Hu Yanfeng)
  E-mail: huyanfenger@tom.com

14.2 CLASS Efficacy and Safety Evaluation Committee

- Responsible for the supervision/monitoring of treatment safety and efficacy of this study.
- Members of CLASS Efficacy and Safety Evaluation Committee:

14.3 CLASS Data Center

- Participates in the design of this study protocol, being responsible for data analysis and statistical interpretation and issuing of statistical reports.
- Responsible for the formulation and provision of CRFs and ECRF (web-based electronic case report forms) and management, storage of research data and maintenance of database.
- Person in charge of CLASS Data Center: Professor Chen Pingyan (Department of Biological Statistics, Southern Medical University)
- Second Person in Charge of Management of Study Data: Lizhen (Beijing Highland

PharmaScience Development Co., Ltd.)

14.4 Data and Safety Monitoring Board

- DSMB is responsible for the supervision of efficacy, safety of this study, supervising all aspects of study performance, validation and approval before release of study results;
- Person in Charge of DSMB: Lizhen (Beijing Highland PharmaScience Development Co., Ltd.)

14.5 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

- Responsible for evaluating this study to determine if risks to which subjects are exposed have been duly minimized and whether these risks are reasonable compared to expected benefits.
- The independent Ethics Committee/Institutional Review Board (IEC/IRB) at the location of each research participating center is responsible for the ethics review of all research participating units.

15. Special Matters

None

16. Publication of Research Results

- The publication of research results should be done on a timely manner adhering to the principles specified in this study protocol.
- Conclusions derived from the main statistical analysis and from other statistical analyses should be published in journals in English after approval of the Efficacy and Safety Evaluation Committee. Manuscripts that do not include analyses of data derived from the study, such as a paper introducing the study, only need consent from the person in charge of the Data Center.
- In terms of authorship of the main published paper on the research results; the main authorship belongs to the Research Committee, followed by the research representative, and the person at the Data Center in charge of statistical analysis for the purpose of publication. The remaining authorship will be ascribed following contribution rules. In the order of respective sample size registration, the Research Responsible Persons of all research participating hospitals are listed as co-authors. All co-authors shall review the paper and agree to publish it before the paper is submitted to the journal. An investigator can at their discretion choose not to be listed as co-author in particular publications.
- If an investigator desires to conduct secondary analyses or analyses for other research purposes based on the overall data collected in the study, he/she must obtain approval from the CLASS Research Committee. An investigator wishing to use data obtained in this study in lectures or other venues should mention the data source and inform the CLASS Research Committee.
- The publication of assumption-related research results aiming at the main research purpose should be completed by the person in charge of research. The publication of assumption-related research results aimed at the secondary research purpose or secondary analytic research results of control data may be negotiated by the person in charge of research participating units of this research organization, but must obtain the permission of the person in charge of research.
- The persons in charge of the research units are the custodians of their own single-center data and should follow privacy rules; the relevant responsibilities for the results, form and content of published single-center data should be self-borne by the person in charge of the Publication Center; however, the CLASS Research Committee does not

assume any responsibility; the use of single-center data must be informed to the CLASS data center who has to provide approval of accuracy; the single-center data of statistical analysis must be marked as derived from this study of the CLASS in order to avoid repeat inclusion at the time of system analysis.

- Without consent of both the Research Committee and the data center, investigators beyond those in the Research Committee cannot directly obtain the overall data and results of statistical analysis of this study from the data center.

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18. Annex

18.1 Informed Consent Form

Multicenter Study on Comparison of Long-term Outcome between Laparoscopic and Open Distal Subtotal Gastrectomy with D2 Lymphadenectomy for Locally Advanced Gastric Cancer (CLASS-01 Trial)

STATISTICAL ANALYSIS PLAN

Version 2.0

Authors: Pingyan Chen, Chongyang Duan

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Contents

Primary Rationale for Amendment:

There was no amendment for the statistical analysis plan in CLASS-01 Trial.

List of abbreviations and definition of terms

AE/SAE	Adverse event / serious adverse event
CI	Confidence interval
CONSORT 2010	Consolidated Standards of Reporting Trials (2010)
EDC	Electronic Data Capture
DFS	Disease free survival
ECG	Electrocardiogram
GCP	Good clinical practice
HR	Heart rate
HREC	Human Research Ethics Committee
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
IQR	Interquartile range
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Authorities
Mins	Minutes
MITT	Modified intention to treat
mmHg	Millimetres of mercury
OR	Odds ratio
PI	Principal Investigator
SD	Standard deviation
BMI	Body-mass index
ECOG	Eastern Cooperative Oncology Group
QoL	quality of life
AGC	Advanced gastric cancer
ASA	American Society of Anesthesiology
AJCC	American Joint Committee on Cancer

Abstract

Background: The prospective randomized controlled multicenter clinical trial (CLASS-01 Trial) is a large-scale investigation of the long-term outcomes of laparoscopic D2 lymphadenectomy compare with open distal subtotal gastrectomy in patients with locally advanced gastric cancer.

Objective: To outline in detail and make public the pre-determined statistical analysis plan (SAP) for the main analyses of CLASS-01 for the primary report of the trial results, and outline subsequent key publications. The SAP was finalised before completion of data collection and is what investigators will adhere to in analysing data.

Methods: All data collected by participating researchers will be reviewed and formally assessed. Information pertaining to the baseline characteristics of patients will be selected and for each item statistically relevant descriptive elements are described. Information relevant to the laparoscopic and open distal subtotal gastrectomy group is classified and, for each item, descriptive statistical analyses are planned for comparisons between the randomised two groups. Finally, for the trial outcomes that are classified as primary, secondary, the most appropriate statistical comparisons to be made between groups are described.

Results: A SAP has been developed for the results of the CLASS-01 study. This plan will allow a comprehensive description of baseline characteristics, features of the trial treatments, along with pre-determined statistical assessment of relevant outcome measures in a way that is transparent, available to the public, verifiable and pre-determined before completion of data collection.

Conclusions: We have developed a pre-determined SAP for the CLASS-01 study which is to be followed, once data are complete, to avoid analysis bias arising from prior knowledge of the study findings.

Trial registration: NCT01609309

1. Introduction

In recent decades, laparoscopic gastrectomy for the treatment of gastric cancer has gained popularity worldwide. Better short-term results, including less pain, earlier mobilization, faster recovery of bowel function, shorten hospital stay, better cosmetic outcomes, and improved quality of life (QoL)[1-5] have been reported for laparoscopic gastrectomy compared to open gastrectomy by several randomized controlled trials (RCTs)[4-9]. Recently, the solid evidences have been established based on well-designed RCTs which demonstrated comparable long-term outcomes for clinical stage I patients between laparoscopic distal gastrectomy (LADG) and open distal gastrectomy (ODG)[3, 10-13]. Thus, laparoscopic gastrectomy has been classified as an optional treatment for cStage I gastric cancer in the recent Japanese Gastric Cancer Treatment Guidelines (4th Edition) [4-9, 14].

However, LADG for advanced gastric cancer (AGC) remains controversial. For locally advanced gastric cancer, several studies have indicated that laparoscopic distal gastrectomy with D2 lymphadenectomy is a technically feasible and safe procedure by experienced surgeons at high-volume specialized centers [1, 15, 16]. To date, a few retrospective studies have reported similar short-term oncologic outcomes of LADG and ODG for the treatment of AGC [10, 15, 17, 18]. However, high-quality evidence regarding long-term oncological outcomes after laparoscopic gastrectomy for AGC is still lacking.

Notably, over 80 percent of all Chinese patients with gastric cancer were diagnosed with advanced disease, and there are more than 400,000 new cases per year in China. With the accumulation of experience in laparoscopic surgery for early gastric cancer since 2003, Chinese surgeons in high-volume institutions attempt to treat AGC patients using the laparoscopic approach. Although multicenter retrospective studies in China demonstrated the surgical safety and short-term efficacy of laparoscopic gastrectomy with D2 lymph node dissection for AGC [16, 19], the application of LADG for AGC is still questioned, mainly due to lack of evidence on long-term oncologic outcome. Therefore, the Chinese laparoscopic gastrointestinal surgery study (CLASS) group launched a multicenter randomized controlled trial (CLASS-01 Trial) to evaluate the long-term ontological outcomes of LADG for the treatment of AGC in September 2012 (NCT01609309).

2. Study design

2.1 Overview

The CLASS-01 study is a prospective, multicentre, randomised, parallel positive control, open labelled clinical trial that compares the long-term outcomes between laparoscopic D2 lymphadenectomy and open distal subtotal gastrectomy in patients with locally advanced gastric cancer (T2-4a, N0-3, M0). The study is registered (ClinicalTrials.gov, NCT01609309) and the first patient was randomised on September, 2012.

The primary aim of the CLASS-01 study is to compare the 3-year disease free survival (DFS) rate of laparoscopic D2 lymphadenectomy against the conventional open distal subtotal gastrectomy. The treatment according to pre-defined treatment protocols.

The null hypothesis is that the laparoscopic surgery is non-inferiority against the conventional open distal subtotal gastrectomy with D2 lymph node dissection for the patients with locally advanced gastric cancer in the 3-year disease free survival rate.

2.2 Patient population

The inclusion/exclusion criteria are kept simple and broad to allow the inclusion of patients with a wide range of characteristics. This not only facilitates recruitment and data collection in a large number of patients as part of routine care, but it also improves the external validity ('generalisability') of the results.

2.2.1 Inclusion criteria

Patients are eligible for inclusion in the study if all of the following criteria are met.

- Age is 18~75 years
- Primary gastric adenocarcinoma confirmed pathologically by endoscopic biopsy
- cT2-4a, N0-3, M0 at preoperative evaluation according to the AJCC Cancer Staging 7th Edition
- Expected curative resection via distal subtotal gastrectomy with D2 lymphadenectomy
- Performance status of 0 or 1 on the ECOG (Eastern Cooperative Oncology Group) scale
- ASA (American Society of Anesthesiology) score class I, II, or III
- Written informed consent is able to be obtained

2.2.2 Exclusion criteria

Patients are excluded from the study if one or more of the following criteria are present.

- Pregnant or breast-feeding women
- Severe mental disorder
- Previous upper abdominal surgery (except laparoscopic cholecystectomy)
- Previous gastrectomy, endoscopic mucosal resection or endoscopic submucosal dissection
- Enlarged or bulky regional lymph node diameter larger than 3 cm based on preoperative imaging
- Other malignant disease within the past five years
- Previous neoadjuvant chemotherapy or radiotherapy
- Unstable angina, myocardial infarction, or cerebrovascular accident within the past six months
- Continuous systematic administration of corticosteroids within one month prior to the study

- Requirement of simultaneous surgery for other diseases
- Emergency surgery due to a complication (bleeding, obstruction or perforation) caused by gastric cancer
- FEV1 (Forced expiratory volume in 1 second) <50% of predicted values

2.3 Randomisation

Eligible patients are randomised using the Pocock-Simon's minimisation algorithm[20] to minimize the difference of age (≤ 60 or > 60 years old), preoperative TNM staging (I, II or III), and histological type (signet-ring cell carcinoma or non-signet-ring cell carcinoma) between the two groups. Randomisation is stratified by centres.

Central randomisation is achieved via a password-protected web-based program operated from The Department of Biostatistics of Southern Medical University in Guangzhou China.

Eighteen surgeons at 17 institutions in China are included in the study according to the Protocol version 1.01 (2013/07/01):

Beijing: Peking University Cancer Hospital (Prof. Xiangqian Su and Prof. Ziyu Li); The People's Liberation Army General Hospital (Prof. Xiaohui Du);

Shanghai: Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (Prof. Weiguo Hu); Zhongshan Hospital, Fudan University (Prof. Yihong Sun); Renji Hospital, Shanghai Jiao Tong University School of Medicine (Prof. Gang Zhao)

Fuzhou: the Affiliated Union Hospital, Fujian Medical University (Prof. Changming Huang); Fujian Provincial Cancer Hospital, Fuzhou (Prof. Mingang Ying);

Guangzhou: Nanfang Hospital, Southern Medical University (Prof. Guoxin Li); The Third Affiliated Hospital of Sun Yat-sen University (Prof. Hongbo Wei); Guangdong General Hospital (Prof. Yong Li)

Harbin: Harbin Medical University Cancer Hospital (Prof. Yingwei Xue);

Wuhan: Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Prof. Kaixiong Tao);

Changchun: The First Hospital, Jilin University (Prof. Jian Suo); The Second Hospital of Jilin University (Prof. Xuedong Fang)

Xi'an: Tangdu Hospital, the Fourth Military Medical University (Prof. Xianli He);

Chengdu: West China Hospital, Sichuan University (Prof. Jiankun Hu).

Nanjing: Nanjing General Hospital of Nanjing Military Command (Prof. Zhiwei Jiang)

Note: Ziyu Li and Xiangqian Su were at the same institution (Beijing University Cancer Hospital).

2.4 Laparoscopic and open distal subtotal gastrectomy with D2 lymphadenectomy

Laparoscopic group Patients allocated to the laparoscopic group are commenced on a laparoscopic distal subtotal gastrectomy with D2 lymph node dissection according to the third English version of the Japanese gastric cancer treatment guideline[21].

Open group Patients allocated to the standard group receive open distal subtotal gastrectomy with D2 lymph node dissection according to the third English version of the Japanese gastric cancer treatment guideline[21].

2.5 Baseline and follow-up assessments

All responsible investigators receive training in the data collection systems and Good Clinical Practice (GCP), and training in the assessment scales if they have had no certification prior to participation. Each collaborating site is required to complete the online screening log, for a randomly assigned calendar month in each participating year, of all patients presenting with a diagnosis of locally advanced gastric cancer who are considered for the study but are subsequently excluded. The screening log records each patient's initials and date of admission together with a brief description of the main reason as to why he or she was not randomised. The log is used to monitor recruitment and identify specific barriers to randomisation of eligible patients.

A detailed list of the assessment schedule is contained in the CLASS-01 protocol and clinical site manuals. Briefly, once informed consent has been obtained, the responsible registered clinician is able to randomise a patient through the secure web-based system after eligibility is confirmed and data are entered for three key baseline clinical variables including age (≤ 60 or > 60 years old), preoperative TNM staging (I, II or III), and histological type (signet-ring cell carcinoma or non-signet-ring cell carcinoma). Socio-demographic and clinical history are then recorded on a baseline form. All data on clinical status, treatment and care are recorded prospectively on special prepared worksheets, and subsequently transferred to electronic data capture (EDC) system on the database. All patients are followed every 3 months for the first 2 years, every 6 months for the 3th years, and annually thereafter, unless death occurs earlier.

The hospital coordinator at each collaborating site ensures that all data are completed in a timely manner. Patients who do not receive the allocated randomised treatment or do not follow the protocol are still followed up and analysed by the 'modified intention to treat' (MITT) principle. Data collection is kept to a minimum to ensure rapid enrolment and follow-up of patients within the context of routine clinical practice.

2.6 Sample size estimation

The sample size was calculated using nQuery Advisor 7.0 (Statistical Solutions Ltd, 4500 Airport Business Park, Cork, Ireland) based on an expected 3-year DFS rate of 72.2% in both groups, and the non-inferiority limit of 10% at a 2.5% of one-tailed significance level with a power of 90%. The sample size was determined as 528 cases in each group under a consideration of not more than 20% dropout rate[22].

The 3-year DFS rate of 72.2% is extrapolated from the results of a prospective study on 3-year DFS compared surgery plus adjuvant chemotherapy with surgery alone for advanced gastric cancer perfomed by Sakuramoto S, et al which published in the N Engl J Med in 2007[23].

2.7 Unblinding

Treatment allocations are open labelled in this study.

2.8 Definitions of the outcomes

2.8.1 Primary outcome

The primary outcome is the 3-year DFS rate.

- Disease-free survival is defined as the time from intervention to disease or death of any cause, and it is censored at the last day when the patient is alive without any evidence of disease.

2.8.2 Secondary outcomes

Secondary outcomes will include the following.

- Morbidity and mortality rates within 30 days after the treatments.
  - *The morbidity and mortality rates* were calculated by dividing the number of affected patients by the total number of recruited patients based on the modified intention-to-treat (MITT) principle.
- 3-year overall survival rate.
  - The 3-year overall survival defined as the time from intervention to the date of death of any cause or last follow-up.
- 3-year recurrence pattern.
  - Recurrence patterns are classified into five categories at the time of first diagnosis: locoregional, hematogenous, peritoneal, distant lymph node, and mixed type.
- Postoperative recovery course.
  - Time to first ambulation, flatus, liquid diet, soft diet, and duration of hospital stay are used to assess the postoperative recovery course, and the amount of abdominal drainage and blood transfusion are also recorded.
- Inflammatory and immune response.
  - The daily highest body temperature before discharge was recorded and the white blood cell count and levels of hemoglobin, C-reactive protein, prealbumin and relevant immune cytokines, including IL-6, and the T cell count, T-helper lymphocyte (CD4+) count, T-suppressor lymphocyte (CD8+) count, natural killer (NK) cell count, B-lymphocyte count, and TNF-α level in peripheral blood were recorded before the operation and on postoperative days 1, 3, and 5

2.8.3 Safety variables

Intra- and post-operative complication is the main adverse event and safety issue.

- The morbidity and mortality were examined within 30 days after surgery. Complications were recorded as follows: intra-abdominal collection and abscess, anastomotic leakage, stenosis, duodenal stump leakage, lymphatic leakage, intraluminal or intra-abdominal bleeding, ileus, pancreatitis, pancreatic fistula, gastroparesis, cholecystitis, wound problems, pneumonia, urinary infection, organ dysfunction, cerebrovascular accident, deep

vein thrombosis, neuropsychiatric disorder, and others. The severity of postoperative complications were assessed according to the Clavien-Dindo classification25.

- A specific complication was diagnosed based on either an image-based physical evaluation or obvious clinical evidence: 1) anastomosis-related complications (leakage, stenosis, or intraluminal bleeding) were confirmed by gastrointestinal X-ray imaging, endoscopy, or angiography; 2) intra-abdominal collections and abscesses were proven by ultrasonography or computed tomography examination and resulted in a systemic inflammatory response for at least 24 hours; 3) both intraoperative major bleeding and postoperative hemorrhage were defined as an amount of hemorrhage exceeding 300 mL; 4) an increased serum amylase level that exceeded three times the upper limit value accompanied by obvious clinical symptoms and signs was classified as traumatic pancreatitis; 5) lymphatic leakage was confirmed with a chyle test when abdominal drainage fluid exceeded 300 mL daily for 5 continuous days after postoperative day 3.
- Discrepancies between reports of the serious adverse event (SAE) by clinician and expert adjudicator are reviewed and resolved by a central expert committee, on review of all available data. SAEs are reported according to standard definitions and coded using terminology of the Medical Dictionary for Regulatory Authorities (MedDRA).

- Other sequelae as reported by clinicians.

3. Funding

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4. Statistical analysis

4.1 Analysis principles

- Analyses will be conducted on an intention-to-treat (ITT) basis. No per-protocol analysis will be carried out as a clear definition of such a dataset is extremely difficult.
- For the primary analysis of DFS, non-inferiority analysis will be used with a one-sided 97.5% confidence interval (CI).

- All the other analyses will be superiority tests with two-sided 95%CI and a type I error of 5%.
- Subgroup analyses will be carried out irrespective of whether there is a significant treatment effect on the primary outcome.
- If missing data is more than trivial (>5% for each covariate), multiple imputation will be carried out.
- Data were coded and entered using electronic data capture (EDC) system on the database.
- Analyses will be conducted primarily using standard statistical software.

4.2 Data sets analysed

- The intent-to-treat data set (*ITT set*) will be constituted of all patients randomised in the study without exclusion and the analysis conducted according to the ITT principle.
- The modified intent-to-treat set (*MITT set*) will be constituted of the subset of ITT set with at least one available primary or secondary outcome after the treatments. This will be used to assess efficacy.
- The per-protocol data set (*PP set*) will be constituted of all randomised patients who fulfil the protocol in terms of the eligibility, interventions, and outcome assessment.
- The safety analysis data set (*SA set*) will be constituted of all randomised patients with safety variables in a format that could be analysed for safety evaluation.

4.3 Interim analyses

There were no planned interim analyses for the primary outcome of 3-year DFS rate.

Two formal interim analyses after approximately 50% and 100% of the patients were enrolled and followed up for 30 days were planned for the secondary outcome of morbidity and mortality rates.

Because the present study is open labelled, the independent DSMB were not organized to keep the data unblinded during interim analyses conduct. Besides the interim analyses weren't designed for the primary outcome, so the type I error were not adjusted in the samples size estimation and for the final analysis. The study was not terminated early.

4.4 Dates, vital status, elimination criteria and consent-related issues

The study is conducted at sites with experienced clinicians. Regionally-based experienced clinical research monitors performed online and on-site data verification. Site monitoring was undertaken, initially after the first few patients were randomised at a site, and thereafter according to number of patient recruited during the course of the trial. As this is an open trial of differing management strategies in a critical illness, monitoring serves to confirm that investigators are adhering to the protocol and Good Clinical Practice (GCP) Guidelines, and should improve the accuracy of the data obtained. Site monitoring aims to confirm: (i) eligibility; (ii) demographic and consent details on all randomised patients; (iii) details of all SAEs against source documents; (iv) collect/correct any outstanding/missing data; and (v) check selected variables against source medical documents in a 10% random selection of patients.

Inconsistencies in key data points, vital status at final follow-up, dates and details of any deaths are queried by the Data and Safety Monitoring Board (DSMB) to limit the number of errors and missing values. Due to the specific circumstances surrounding emergency care research it may not always be possible to obtain consent from either the patient or next of kin without delaying the initiation of treatment. In the situation where a patient is unable to give consent and a next of kin or other person responsible is not available or cannot be contacted, and with approval of the local ethics committee, clinicians may enrol eligible patients and inform the patient or their person responsible for the patient as soon as possible so that delayed consent

can be requested. The reasons for being unable to obtain prior consent will be documented, dated, and signed in the patient's file. If the patient should die or continue to be unable to give informed consent at the end of the follow up period, the next of kin or person responsible should be approached to obtain delayed consent. In the case of a patient's death, the site Principal Investigator will use discretion on a case by case basis before contacting the next of kin or surrogate, in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient or person responsible consent will be documented in the patients file.

Some important situations can lead to cessation of the study treatment:

- Intra- or postoperative examine reveals metastasis (M1) and / or cytology positive
- Enlarged or bulky regional lymph node surrounds targeted vessels resulting in impossibility of R0 resection
- Total gastrectomy must be done to ensure negative proximal resection margin
- Emergency situation (intolerance to surgery or anesthesia) after enrollment
- Requirement of performing emergency surgery after enrolment
- Withdrawing the study due to patient's personal reasons after enrollment
- Proved to have violated the protocol

In all cases, the study treatment will cease and the patient will receive appropriate treatment as determined by the attending clinician. The information sheet provided to the patient and/or the next of kin or surrogate clearly states that the patient can be withdrawn from the study at any time without prejudice and explanation. Such withdrawal is documented in the patient's file. If withdrawal of consent relates to the treatments alone, data collection can continue on documentation of this fact in the patient's files. If consent for use of all data is withheld, the patient's data will be removed from the analysis, except for data related to consent. If consent for future study inclusion is withdrawn, the patient's data will be included up to the date the consent was withdrawn. Censoring dates will be used only in case of 'real' loss to follow-up, such that the date of censoring will be the last day of contact, or the date of hospital discharge if no other information is available.

4.5 Trial profile

Flow of patients through the study will be displayed in a CONSORT diagram (Appendix 2; Figure 1). The report will include the number of screened patients who met the inclusion criteria and the number included, and reasons for exclusion of non-included patients. In addition, the number of patients randomised outside the time window and other significant protocol deviations will be provided.

4.6 Patients characteristics and baseline comparisons

Description and statistical inference of the following baseline characteristics will be presented by treatment group.

Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data is available. If missing values are ⩾5%, the denominator will be added in a footnote in the corresponding summary table. In some instances, frequencies and percentage of patients in the category will be reported as further indicated in the tables. Continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean and standard deviation [Mean ± SD] for variables identified with #, or median and 25%, 75% quartiles [Median(IQR)] with †. Durations will also be summarised by medians and IQR.

Statistical inference of normally distributed continuous variables were performed using t-tests; non-normally distributed continuous variables were analysed using Wilcoxon rank-sum tests. The Pearson chi-square test or Fisher exact test were used, as appropriate, for categorical data.

Baseline measures for all patients will be tabulated for the following variables: demographics and pathological characteristics.

4.7 Operation details and postoperative recovery course

Operation details will be summarised by treatment arm. Counts and percentages will be displayed for all categorical items. Continuous outcomes will be summarised by either means (SD) or medians (IQR) as further detailed in the same table.

4.8 Primary outcome

The non-inferiority test for the primary outcome of 3-year DFS rate will be conducted by comparing the lower bound of the one-sided 97.5%CI with the non-inferiority limit of -10% (laparoscopic vs open). The one-sided 97.5%CI was calculated by Newcombe's method that recommended by FDA and NCCLS. Frequencies and percentages per arm will also be reported.

For the secondary analyses of DFS, we will firstly estimate the hazard ratio (HR) using mixed effects Cox regression with site treated as the random effect. We will also perform a multivariable mixed effects Cox regression adjusted for key prognostic covariates that are significantly associated with DFS in univariable analyses. Candidate variables include age (≤ 60 or > 60 years old), sex, body mass index, Eastern Cooperative Oncology Group score (0 or >0), comorbidity (yes or no), preoperative TNM staging (I, II or III), histological type (signet-ring cell carcinoma or non-signet-ring cell carcinoma), and adjuvant chemotherapy (yes or no).

4.9 Missing values in the primary endpoint

The missing data for the 3-year DFS will not be imputed, unless differential loss-to-follow-up is suspected. Instead, a secondary analysis based on survival methods will be performed and the missing data will be treated as censored data.

4.10 Secondary outcomes

For the secondary outcome of OS, mixed effects Cox regression with site treated as the random effect will be used. A multivariable mixed effects Cox regression will also be undertaken adjusted for key prognostic covariates that are significantly associated with OS in univariable analyses. Candidate variables include age (≤ 60 or > 60 years old), sex, body mass index, Eastern Cooperative Oncology Group score (0 or >0), comorbidity (yes or no), preoperative TNM staging (I, II or III), histological type (signet-ring cell carcinoma or non-signet-ring cell carcinoma), and adjuvant chemotherapy (yes or no). For the secondary outcome of recurrence, competing risks survival regression will be used with deaths treated as the competing events.

All the other binary secondary outcomes will be preferably analysed by means of a χ^2 test. A Fisher test will be used if the expected numbers are ≤5. These data will be summarised by an odd ratio (OR) and its 95% CI.

Skewed continuous endpoints, such as the counts of T lymphocyte, will all be summarised by medians (IQR). The effect of treatment will be tested by a Wilcoxon test. A difference between medians and its 95% CI will be imputed if deemed useful.

4.11 Safety endpoints

Counts and percentages per treatment arm will generally summarise all specific pre-defined SAE categories. They generally represent the number of patients experiencing a specific SAE (at least once), the fatal ones, and the breakdown by subcategory (when appropriate). This includes morbidity and mortality. The exact definitions based on MedDRA codes have been established prior to interim analysis and are available upon

request. If possible a global χ^2 or Fisher test of a treatment effect will be carried out and its p value reported. A Fisher exact test will be performed only when the χ^2 test is thought to be unreliable due to small expected numbers per cell (Appendix 3, Table 3). A measure of treatment effect (i.e. a relative risk and its 95% CI) might be reported if its computation is possible (Appendix 1, Table 4). None of the above analyses will be adjusted.

4.12 Subgroup analysis

All subgroups will be defined by the presence or absence of a pre-randomisation variable; we will not select any subgroups based on post-randomisation criteria. Unadjusted p values will be reported but the number of declared subgroups analyses will be specified in all publications. Categorisation is as follows:

- age category: ⩽60, >60 years
- pathological staging (AJCC-7): Ⅰ, II and Ⅲ
- histological type: signet ring cell carcinoma, non-signet ring cell carcinoma

The main analysis for each subgroup will be an interaction test in a cox regression model to determine whether the effect of treatment differs significantly across categories for that particular subgroup. Summary measures will include counts, percentages and a measure of effect (HR) with its 95% CI obtained in a stratified analysis, and reported with a p-value for the interaction test. Forest plots will be constructed to illustrate subgroup analyses, with p values for heterogeneity for each pair of subgroups.

4.13 Tables and figures for main paper

The proposed tables and figures for the main results are presented in Appendix 1 and 2. Appendix 3 includes supplementary data tables. Table 1 will report key collected baseline characteristics of the participants by treatment group. Table 2 will report on the operation details and postoperative recovery course. Table 3 will report on pathological characteristics. Table 4 will report the primary and secondary outcomes, and major adverse events. Table 5 will report the inflammatory and immune response. Supplementary Table 3 (Appendix 3) will report all non-fatal serious adverse events to the end of follow-up. In addition, the following figures will be prepared:

- A CONSORT diagram illustrating the flow of patients through the study (Appendix 2; Figure 1)
- Kaplan-Meier survival curve for DFS rate (Appendix 2, Figure 2).
- Kaplan-Meier survival curve for OS rate (Appendix 2, Figure 3).
- Cumulative incidence for first time recurrence (Appendix 2, Figure 4).
- A forest plot of the treatment effect on the primary outcome among different subgroups of all baseline and postoperative variables (Appendix 1, Table 6).

A more extensive list of tables and figures used to report additional information on the CLASS-01 has been written and is available upon request.

4.14 Proposed content of primary and subsequent publications

Appendix 4 provides an outline of the publication plan for the CLASS-01 trial, alone and when combined with data from CLASS-01.

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Appendix 1: Proposed format of data tables in the main results publication

Table 1: Baseline characteristics of the study participants

Characteristic	Open group (n=xxxx)	Laparoscopic group (n=xxxx)	P values
Demographic and clinical			
Basic data			
Age (yr), mean (SD)	xx (xx)	xx (xx)	
Male, n (%)	xxx (xx)	xxx (xx)	
Height (cm), mean (SD)	xx (xx)	xx (xx)	
Body Weight (kg), mean (SD)	xx (xx)	xx (xx)	
BMI (Kg/M^2), mean (SD)	xx (xx)	xx (xx)	
Body Temperature (℃), mean (SD)	xx (xx)	xx (xx)	
Breathing (times/minutes), mean (SD)	xx (xx)	xx (xx)	
Heart rate (beats per minute), mean (SD)	xxx (xx)	xxx (xx)	
Systolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)	
Diastolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)	
Past history of surgery			
History of abdominal surgery, n (%)	xxx (xx)	xxx (xx)	
Main comorbidity within past 6 months			
Diabetes, n (%)	xxx (xx)	xxx (xx)	
Coronary artery disease, n (%)	xxx (xx)	xxx (xx)	
Hypertension, n (%)	xxx (xx)	xxx (xx)	
Heart failure, n (%)	xxx (xx)	xxx (xx)	
Chronic obstructive pneumonia , n (%)	xxx (xx)	xxx (xx)	
Chronic hepatitis and hypohepatia, n (%)	xxx (xx)	xxx (xx)	
Chronic renal disease and renal failure, n (%)	xxx (xx)	xxx (xx)	
Cirrhosis of liver, n (%)	xxx (xx)	xxx (xx)	
Cerebrovascular accident, n (%)	xxx (xx)	xxx (xx)	
Immunological disease, n (%)	xxx (xx)	xxx (xx)	
Long-term use of immunosuppressor, n (%)	xxx (xx)	xxx (xx)	
Others, n (%)	xxx (xx)	xxx (xx)	
Associated Symptoms			
Obstruction, n (%)	xxx (xx)	xxx (xx)	
Perforation, n (%)	xxx (xx)	xxx (xx)	
Bleeding, n (%)	xxx (xx)	xxx (xx)	
Hemorrhagic anemia, n (%)	xxx (xx)	xxx (xx)	
Others, n (%)	xxx (xx)	xxx (xx)	
ECOG score			
Median (IQR)	xxx (xx)	xxx (xx)	

0, n (%)	xxx (xx)	xxx (xx)	
1, n (%)	xxx (xx)	xxx (xx)	
2, n (%)	xxx (xx)	xxx (xx)	
3, n (%)	xxx (xx)	xxx (xx)	
4, n (%)	xxx (xx)	xxx (xx)	
5, n (%)	xxx (xx)	xxx (xx)	
ASA score			
Ⅰ, n (%)	xxx (xx)	xxx (xx)	
Ⅱ, n (%)	xxx (xx)	xxx (xx)	
Ⅲ, n (%)	xxx (xx)	xxx (xx)	
Ⅳ n (%)	xxx (xx)	xxx (xx)	
Ⅴ, n (%)	xxx (xx)	xxx (xx)	

Table 2: Operation details and intraoperative complication

Characteristic	Open group (n=xxxx)	Laparoscopic group (n=xxxx)	P values
Operative data			
Operation time（mins）, mean (SD)	xxx (xx - xx)	xxx (xx - xx)	
Blood loss（ml）, mean (SD)	xxx (xx - xx)	xxx (xx - xx)	
Blood transfusion, n (%)	xxx (xx)	xxx (xx)	
Length of incision（cm）, mean (SD)	xxx (xx - xx)	xxx (xx - xx)	
Conversion to open surgery, n (%)	xxx (xx)	xxx (xx)	
Combined resection, n (%)	xxx (xx)	xxx (xx)	
Distal gastrectomy, n (%)	xxx (xx)	xxx (xx)	
D2 lymphadenectomy, n (%)	xxx (xx)	xxx (xx)	
Reconstruction			
B-I	xxx (xx)	xxx (xx)	
B-II	xxx (xx)	xxx (xx)	
Roux-en-Y	xxx (xx)	xxx (xx)	
Others	xxx (xx)	xxx (xx)	
Recovery course			
Time to ambulation（days）, median/mean (IQR/SD)	xxx (xx - xx)	xxx (xx - xx)	
Time to first flatus（days）, median/mean (IQR/SD)	xxx (xx - xx)	xxx (xx - xx)	
Time to liquid intake days）, median/mean (IQR/SD)	xxx (xx - xx)	xxx (xx - xx)	
Hospital stay（day）, median/mean (IQR/SD)	xxx (xx - xx)	xxx (xx - xx)	
Intraoperative complications			
Total intraoperative complications, n (%)	xxx (xx)	xxx (xx)	
Death, n (%)	xxx (xx)	xxx (xx)	
Bleeding（>400ml）, n (%)	xxx (xx)	xxx (xx)	
Injury of digestive tract, n (%)	xxx (xx)	xxx (xx)	
Injure of biliary tract, n (%)	xxx (xx)	xxx (xx)	
Injure of pancreas and spleen, n (%)	xxx (xx)	xxx (xx)	
Injure of other organs, n (%)	xxx (xx)	xxx (xx)	
Trocar-related injury, n (%)	xxx (xx)	xxx (xx)	
Hypercapnia, n (%)	xxx (xx)	xxx (xx)	
Anaesthesia-related, n (%)	xxx (xx)	xxx (xx)	
Others, n (%)	xxx (xx)	xxx (xx)	

Table 3: Postoperative pathological data

Characteristic	Open group (n=xxxx)	Laparoscopic group (n=xxxx)	P values
Tumor location			
Vertical axis			
L, n (%)	xxx (xx)	xxx (xx)	
M, n (%)	xxx (xx)	xxx (xx)	
L and M, n (%)	xxx (xx)	xxx (xx)	
Horizontal axis			
Anterior, n (%)	xxx (xx)	xxx (xx)	
Posterior, n (%)	xxx (xx)	xxx (xx)	
Lesser curvature, n (%)	xxx (xx)	xxx (xx)	
Greater curvature, n (%)	xxx (xx)	xxx (xx)	
Circumference, n (%)	xxx (xx)	xxx (xx)	
Tumor size			
Maximum length（cm）, median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Minimum length（cm）, median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Pathological types（WHO）			
Papillary adenocarcinoma, n (%)	xxx (xx)	xxx (xx)	
Tubular adenocarcinoma, n (%)	xxx (xx)	xxx (xx)	
Mucinous adenocarcinoma, n (%)	xxx (xx)	xxx (xx)	
Signet ring cell carcinoma, n (%)	xxx (xx)	xxx (xx)	
Poorly differentiated, n (%)	xxx (xx)	xxx (xx)	
Others, n (%)	xxx (xx)	xxx (xx)	
Histology			
G1, n (%)	xxx (xx)	xxx (xx)	
G2, n (%)	xxx (xx)	xxx (xx)	
G3, n (%)	xxx (xx)	xxx (xx)	
G4, n (%)	xxx (xx)	xxx (xx)	
Gx, n (%)	xxx (xx)	xxx (xx)	
Exfoliocytology			
CY+, n (%)	xxx (xx)	xxx (xx)	
CY-, n (%)	xxx (xx)	xxx (xx)	
CYx, n (%)	xxx (xx)	xxx (xx)	
Immunohistochemistry			
Her-2, n (%)	xxx (xx)	xxx (xx)	
Fish, n (%)	xxx (xx)	xxx (xx)	

VEGF, n (%)	xxx (xx)	xxx (xx)	
EGFR, n (%)	xxx (xx)	xxx (xx)	
Pathological tumour stage（AJCC-7）			
IA, n (%)	xxx (xx)	xxx (xx)	
IB, n (%)	xxx (xx)	xxx (xx)	
IIA, n (%)	xxx (xx)	xxx (xx)	
IIB, n (%)	xxx (xx)	xxx (xx)	
IIIA, n (%)	xxx (xx)	xxx (xx)	
IIIB, n (%)	xxx (xx)	xxx (xx)	
IIIC, n (%)	xxx (xx)	xxx (xx)	
IV, n (%)	xxx (xx)	xxx (xx)	
Pathological T stage			
T0, n (%)	xxx (xx)	xxx (xx)	
Tis, n (%)	xxx (xx)	xxx (xx)	
T1, n (%)	xxx (xx)	xxx (xx)	
T1a, n (%)	xxx (xx)	xxx (xx)	
T1b, n (%)	xxx (xx)	xxx (xx)	
T2, n (%)	xxx (xx)	xxx (xx)	
T3, n (%)	xxx (xx)	xxx (xx)	
T4, n (%)	xxx (xx)	xxx (xx)	
T4a, n (%)	xxx (xx)	xxx (xx)	
T4b, n (%)	xxx (xx)	xxx (xx)	
Tx, n (%)	xxx (xx)	xxx (xx)	
Pathological N stage			
N0, n (%)			
N1, n (%)			
N2, n (%)	xxx (xx)	xxx (xx)	
N3, n (%)	xxx (xx)	xxx (xx)	
N3a, n (%)	xxx (xx)	xxx (xx)	
N3b, n (%)	xxx (xx)	xxx (xx)	
Nx, n (%)	xxx (xx)	xxx (xx)	
Pathological M stage			
M0, n (%)	xxx (xx)	xxx (xx)	
M1, n (%)	xxx (xx)	xxx (xx)	
Mx, n (%)	xxx (xx)	xxx (xx)	
Lymph node harvested, median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Metastatic lymph nodes, median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Stomach			
Length of greater curvature (cm), median	xxx (xx - xx)	xxx (xx - xx)	

(IQR)			
Length of lesser curvature (cm), median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Resection margin			
Positive proximal, n (%)	xxx (xx)	xxx (xx)	
Positive distal, n (%)	xxx (xx)	xxx (xx)	
Length of resection margin			
Proximal (cm), median (IQR)	xxx (xx - xx)	xxx (xx - xx)	
Distal (cm), median (IQR)	xxx (xx - xx)	xxx (xx - xx)	

Table 4: Clinical endpoints at 3 years

Outcome	Open group (n=xxxx)	laparoscopic group (n=xxxx)	Treatment effect (95% CI)	P value
Primary endpoint				
Disease free survival rate				
Primary analysis, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Secondary analysis, median (IQR) †	xxx (xx~xx)	xxx (xx~xx)	xxx (xxx-xxx)#	0.xxx
Secondary endpoints				
Morbidity and mortality rates, n (%)	xxx (xx)	xx (xx)	xxx (xxx-xxx)^	0.xxx
30 days	xxx (xx)	xx (xx)		
3 months	xxx (xx)	xx (xx)		
6 months	xxx (xx)	xx (xx)		
9 months	xxx (xx)	xx (xx)		
12 months	xxx (xx)	xx (xx)		
15 months	xxx (xx)	xx (xx)		
18 months	xxx (xx)	xx (xx)		
21 months	xxx (xx)	xx (xx)		
24 months	xxx (xx)	xx (xx)		
30 months	xxx (xx)	xx (xx)		
36 months	xxx (xx)	xx (xx)		
Death, n (%)	xxx (xx)	xx (xx)	xxx (xxx-xxx)^	0.xxx
Overall survival rate, median (IQR) †	xxx (xx~xx)	x (xx~xx)	xxx (xxx-xxx)#	0.xxx
Primary cause of death, n (%)				
Tumor-related	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Other tumor-related	xxx (xx)	xxx (xx)		
Non tumor-related	xxx (xx)	xxx (xx)		
Other causes	xxx (xx)	xxx (xx)		
Recurrence, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)^	0.xxx

First time to recurrence, median (IQR) †	xxx (xx~xx)	xxx (xx~xx)	xxx (xxx-xxx)#	0.xxx
Site of recurrence†				
Local,n (%)	xxx (xx)	xxx (xx)		
Residual stomach, n (%)	xxx (xx)	xxx (xx)		
Anastomosis, n (%)	xxx (xx)	xxx (xx)		
Stump of duodenum, n (%)	xxx (xx)	xxx (xx)		
Regional lymph node, n (%)	xxx (xx)	xxx (xx)		
Peritoneum, n (%)	xxx (xx)	xxx (xx)		
Peritoneal implantation, n (%)	xxx (xx)	xxx (xx)		
Krukenberg's tumor, n (%)	xxx (xx)	xxx (xx)		
Haematogenous metastasis, n (%)	xxx (xx)	xxx (xx)		
Distant lymph node metastasis, n (%)	xxx (xx)	xxx (xx)		
Mixed, n(%)				
Safety				
Total number of adverse events (AE), n (%)‡	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Number of patients with at least one AE, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Total number of serious adverse events (SAE), n (%)‡	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx
Number of patients with at least one SAE, n (%)	xxx (xx)	xxx (xx)	xxx (xxx-xxx)*	0.xxx

*Odds ratio, # Hazard ratio, using log rank test, † For survival time, ‡A patient could have more than one site.

Table 5: Inflammatory and immune response

Outcome	Baseline	1 day	3 days	5 days	P Value
Inflammatory response, CRP					$P_{time*group}$=0.xxx
Standard Group, median (IQR)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	xx.xx(xx.xx~xx.xx)	P_{group}=0.xxx
Immune response					
IL-6,					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
T lymphocyte					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
CD4					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
CD8					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
NK					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx

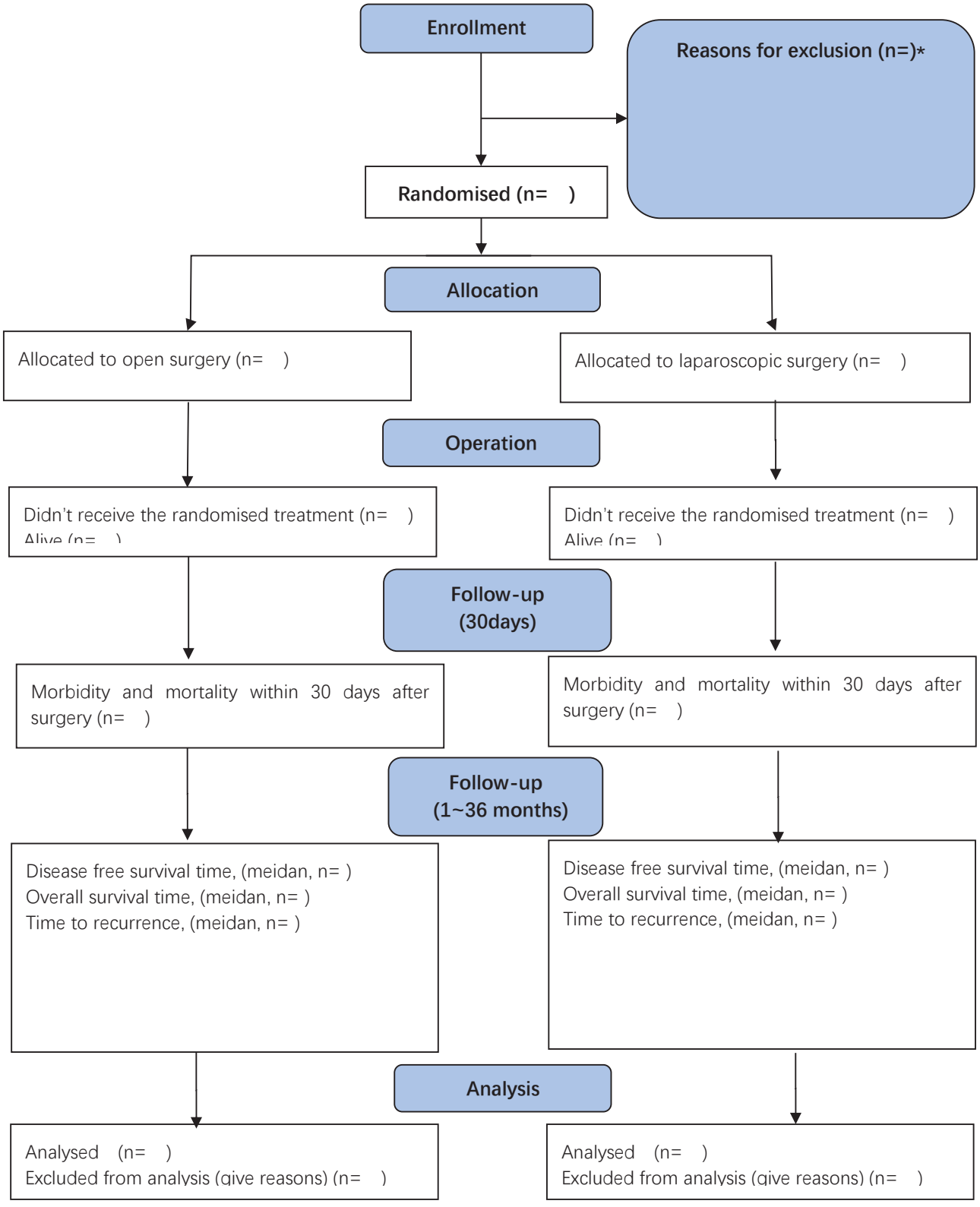
B lymphocyte					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
CD4/CD8					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx
TNF-α					$P_{time*group}$=0.xxx
Standard Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{time} =0.xxx
Early intensive Group, mean (SD)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	xx.xx(xx.xx)	P_{group}=0.xxx

Table 6: Forest plot of key subgroups

	Open group (n=xxx)	laparoscopic group (n=xxx)	Odds ratio (95% CI)	p-value fo interaction
Age				0.xxx
≤ 60 years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
60+ years	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
AJCC-7				0.xxx
I	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
II	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
III	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Histological types				0.xxx
Signet ring cell	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Non-signet-ring cell	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
Institutions				0.xxx
01	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
02	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
03	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	
…	xxx (xx)	xxx (xx)	xxx (xxx-xxx)	

Appendix 2: Figures for the main results paper

Figure 1: CLASS-01 Flow Diagram based on CONSORT 2010



*Screening logs collected at each site 1 month per year

Figure 2: Kaplan–Meier curve for comparison of 3-year disease free survival rate between two groups

Figure 3: Kaplan–Meier curve for comparison of 3-year overall survival rate between two groups

Figure 4: Cumulative incidence curve for comparison of first time recurrence within 3 years after the surgery between two groups

Appendix 3: Proposed format of data tables in interim analysis

Table 1: Baseline characteristics of the study participants

Characteristic	Open group (n=xxxx)	Laparoscopic group (n=xxxx)	P values
Demographic and clinical			
Basic data			
Age (yr), mean (SD)	xx (xx)	xx (xx)	
Male, n (%)	xxx (xx)	xxx (xx)	
Height (cm), mean (SD)	xx (xx)	xx (xx)	
Weight (kg), mean (SD)	xx (xx)	xx (xx)	
BMI (Kg/M^2), mean (SD)	xx (xx)	xx (xx)	
Temperature (℃), mean (SD)	xx (xx)	xx (xx)	
Breathing (times/minutes), mean (SD)	xx (xx)	xx (xx)	
Heart rate (beats per minute), mean (SD)	xxx (xx)	xxx (xx)	
Systolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)	
Diastolic BP (mmHg), mean (SD)	xxx (xx)	xxx (xx)	
Past history of surgery			
History of abdominal surgery, n (%)	xxx (xx)	xxx (xx)	
Main comorbidity within past 6 months			
Diabetes, n (%)	xxx (xx)	xxx (xx)	
Coronary artery disease, n (%)	xxx (xx)	xxx (xx)	
Hypertension, n (%)	xxx (xx)	xxx (xx)	
Heart failure, n (%)	xxx (xx)	xxx (xx)	
Chronic obstructive pneumonia , n (%)	xxx (xx)	xxx (xx)	
Chronic hepatitis and hypohepatia, n (%)	xxx (xx)	xxx (xx)	
Chronic renal disease and renal failure, n (%)	xxx (xx)	xxx (xx)	
Cirrhosis of liver, n (%)	xxx (xx)	xxx (xx)	
Cerebrovascular accident, n (%)	xxx (xx)	xxx (xx)	
Immunological disease, n (%)	xxx (xx)	xxx (xx)	
Long-term use of immunosuppressor, n (%)	xxx (xx)	xxx (xx)	

Others, n (%)	xxx (xx)	xxx (xx)	
Associated Symptoms			
Obstruction, n (%)	xxx (xx)	xxx (xx)	
Perforation, n (%)	xxx (xx)	xxx (xx)	
Bleeding, n (%)	xxx (xx)	xxx (xx)	
Hemorrhagic anemia, n (%)	xxx (xx)	xxx (xx)	
Others, n (%)	xxx (xx)	xxx (xx)	
ECOG score			
Median (IQR)	xxx (xx)	xxx (xx)	
0, n (%)	xxx (xx)	xxx (xx)	
1, n (%)	xxx (xx)	xxx (xx)	
2, n (%)	xxx (xx)	xxx (xx)	
3, n (%)	xxx (xx)	xxx (xx)	
4, n (%)	xxx (xx)	xxx (xx)	
5, n (%)	xxx (xx)	xxx (xx)	
ASA score			
Ⅰ, n (%)	xxx (xx)	xxx (xx)	
Ⅱ, n (%)	xxx (xx)	xxx (xx)	
Ⅲ, n (%)	xxx (xx)	xxx (xx)	
Ⅳ n (%)	xxx (xx)	xxx (xx)	
Ⅴ, n (%)	xxx (xx)	xxx (xx)	

Table 2: Morbidity and mortality details at 30 days, number (%)

Characteristic	Open group (n=xxxx)	laparoscopic group (n=xxxx)
Total	xxx (xx)	xxx (xx)
Wound infection	xxx (xx)	xxx (xx)
Fluid collection/abscess	xxx (xx)	xxx (xx)
Intra-abdominal Bleeding	xxx (xx)	xxx (xx)
Intraluminal bleeding	xxx (xx)	xxx (xx)
Ileus	xxx (xx)	xxx (xx)
Intestinal fistula	xxx (xx)	xxx (xx)
Anastomotic stenosis	xxx (xx)	xxx (xx)
Anastomotic leakage	xxx (xx)	xxx (xx)
Lymphatic leakage	xxx (xx)	xxx (xx)
Stasis	xxx (xx)	xxx (xx)

Pancreatic leakage	xxx (xx)	xxx (xx)
Pancreatitis	xxx (xx)	xxx (xx)
Pneumonia	xxx (xx)	xxx (xx)
Urinary infection	xxx (xx)	xxx (xx)
Renal failure	xxx (xx)	xxx (xx)
Hepatic failure	xxx (xx)	xxx (xx)
Cerebrovascular complication	xxx (xx)	xxx (xx)
cardiovascular complication	xxx (xx)	xxx (xx)
Deep vein thrombosis	xxx (xx)	xxx (xx)
Others	xxx (xx)	xxx (xx)

Table 3: Serious adverse events at 30 days, number (%)

	Open group (n=xxxx)	**laparoscopic group (n=xxxx)**	**P value***
SAEs	**n (%)**	**n (%)**	
*Total events***	xxx (xx)	xxx (xx)	0.xxx
Number of patients	xxx (xx)	xxx (xx)	0.xxx
...	xxx (xx)	xxx (xx)	0.xxx
Other SAE	xxx (xx)	xxx (xx)	0.xxx

Counts correspond to the number of patients who experienced at least one specific SAE with the exception of the first row. Denominators are all patients randomised.

* Chi-square or Fisher test if an expected cell count is lower than 5. If the total number of events is 0 the test is not required.

**A patient could have more than one event

Appendix 4: Proposed content of primary and key subsequent publications

	Content / overview of analytic approach
1	*Interim analysis 1:* when approximately 50% of the patients were enrolled and followed up for 30 days, safety analysis will be performed for the two groups
2	*Interim analysis 2:* when all of the patients were enrolled and followed up for 30 days, morbidity and mortality rate will be compared between the two groups
3	*Main results paper 1:* when all of the patients were followed up for 3 years after operation, 3-year disease-free survival will be compared between the two groups

Appendix 5: Statement of contribution of the authors

Prof. Pingyan Chen and Chongyang Duan participated in writing the first draft and all revisions of the SAP. All the members of the CLASS group participated in critical reviews of the SAP. Finally, the SAP was approved by the CLASS-01 Executive Committee. The SAP was prepared without knowledge of the data. The study statisticians prepared tabulations of the baseline characteristic as grouped data for reports during the course of the study, which were used to inform the authors in selection of cut-points to define subgroups and aspects of the overall analysis plan. The SAP was prepared independent of the key funding agency for the trial, the Program of Global Medical Affairs Department, Johnson & Johnson Medical Ltd..