CLASS02 TRIAL PROTOCOL

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Prospective Randomized Controlled Multicenter Clinical Trial For Comparison Of Safety Between Laparoscopic And Open Total Gastrectomy In Patients With Clinical Stage I Gastric Cancer

CLASS02 cStage I. GC. TG. Lap. Vs. Open

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Summary

Protocol Title	Prospective Randomized Controlled Multicenter Clinical Trial For Comparison Of Safety Between Laparoscopic And Open Total Gastrectomy In Patients With Clinical Stage I Gastric Cancer
Protocol Version	Version 3.0
Sponsor	Yihong Sun
Research Center Number	13
Research Centers	Zhongshan Hospital, Fudan University Fudan University Shanghai Cancer Center Nangfang Hospital, Southern Medical University The First Hospital Affiliated to AMU Renji Hospital, Shanghai Jiao Tong University Beijing Cancer Hospital, Peking University Chinese PLA General Hospital West China Hospital, Sichuan University Fujian Medical University Union Hospital The First Affiliated Hospital of Fujian Medical University The First Hospital of Jilin University The First Affiliated Hospital with Nanjing Medical University Guangdong General Hospital
Indications	Patients with clinical stage I gastric adenocarcinoma in the upper and middle of their stomach
Research Purpose	This study aims to determine the safety of LTG (Laparoscopic Total Gastrectomy) compared with OTG (Open Total Gastrectomy) with D1+/D2 lymphadenectomy for clinical stage I (T1N0M0、T1N1M0、T2N0M0) gastric adenocarcinoma.
Research Design	Prospective, multicenter, randomized, controlled, open, non-inferiority verification

Case Grouping	• Group A (study group): Laparoscopic total gastrectomy • Group B (control group): Open total gastrectomy
Sample Size	It is a non-inferiority verification study on clinical safety, with the early operative morbidity and mortality rate as the primary outcome. According to the previous reports, the morbidity rate is about 20% and 15% for OTG group and LTG group, respectively. Setting one-side $\alpha = 0.025$, $\beta = 0.2$, and the non-inferiority margin $\delta = 10\%$, the sample size required for each group is 100 cases. Considering that the maximum dropout rate for this clinical study is about 10%, the sample size is determined as 112 cases in each group.
Inclusion Criteria	● Aged 18-75 years ● Primary lesion is pathologically diagnosed as gastric adenocarcinoma ● Clinical stage IA (T1N0M0) or IB (T1N1M0, T2N0M0) according to AJCC-7th TNM staging system ● Tumor located in the upper or middle third of the stomach ● No invasion to Z-line ● Curative resection is expected to be achievable by total gastrectomy with D1+/D2 lymphadenectomy ● BMI < 30 kg/m^2 ● ECOG PS 0 or 1 ● ASA class: I, II, or III ● Sufficient organ functions ● Written informed consent
Exclusion Criteria	● Preoperative examination indicate enlargement of perigastric or retroperitoneal lymph nodes(≥1.0cm) ● Preoperative neoadjuvant chemotherapy or radiotherapy ● Previous history of upper abdominal surgery (except for laparoscopic cholecystectomy)

	● Women during pregnancy or breast-feeding ● Synchronous or metachronous (within 5 years) malignancies ● Body temperature ≥ 38℃ before surgery or infectious disease with a systemic therapy indicated ● Severe mental disease ● Severe respiratory disease ● Severe hepatic and renal dysfunction ● Unstable angina pectoris or history of myocardial infarction within 6 months ● History of cerebral infarction or cerebral hemorrhage within 6 months ● Continuous systemic steroid therapy within 1 month (except for topical use) ● Gastric cancer complications (bleeding, perforation, obstruction) that requiring emergency surgery ● Patients are participating or have participated in another clinical trial (within 6 months)
Withdraw Criteria	● Confirmed that the stage of the disease is stage IV intraoperatively/postoperatively; ● Confirmed that it is unable to complete R0 resection due to the disease progression intraoperatively; ● Confirmed that there are obviously enlargement of splenic hilar lymph nodes intraoperatively; ● Confirmed that it only needs to perform distal gastrectomy intraoperatively; ● Patients requiring simultaneous surgical treatment for other diseases (except cholecystolithiasis); ● Sudden severe comorbidities in the perioperative period (intolerable surgery or anesthesia), which are unsuitable or

	unable to implement the treatment protocol of this study as scheduled; ● Patients are confirmed to require emergency surgery according to the condition changes verified by attending doctors after being enrolled in this study; ● Patients are voluntary to quit or discontinue treatment due to personal reasons in any stage after being enrolled in this study; ● Treatment that proved to violate the study protocol.
Intervention	Total gastrectomy, D1+/D2-10 lymphadenectomy according to Japanese Gastric Cancer Treatment Guideline (Fourth edition, May. 2014) • Group A: Laparoscopic total gastrectomy • Group B: Open total gastrectomy
Endpoint	Primary Endpoint: • Early operative morbidity and mortality rate [Time frame: 30 days after the operation (postoperative hospital stay ≤ 30 days) or operation to first discharge from hospital (postoperative hospital stay > 30 days)] Secondary Endpoint: • Postoperative recovery courses [Time frame: Operation to first discharge from hospital] • Postoperative hospital stays [Time frame: Operation to first discharge from hospital]
Statistical considerations	● Statistical software: SAS statistical software. ● Descriptive statistics: ■ Continuous data: number of cases (number of missing cases), mean, median, standard deviation, P25, P75, minimum and maximum; ■ Categorical data: frequency and the corresponding

	percentages. For primary safety endpoint, calculate the 95% CI in addition to the percentage. ● Statistical inference: unless otherwise specified, the two-sided P ≤0.05 indicates statistically significant differences between the two groups. ■ Non-inferiority statistical inference for primary endpoint: if the upper limit of the 95% confidence interval (95%CI) for the difference of OTG-group incidence rate - LTG-group incidence rate was less than 10%, it could be inferred that LTG was not inferior to OTG in the incidence of early complications. ■ Statistical analysis for baseline variables and secondary endpoints: continuous variables were examined by independent sample t-test or Wilcoxon rank-sum test, and categorical variables were compared by Pearson chi-square test, Fisher's exact test or CMH chi-square test as appropriate. ■ Analysis of withdrawn patients: the number of patients who are enrolled, withdrawn, removed, completed, and number of every analysis set will be listed. ● Stratified analysis for primary safety endpoint: Types of complications and the Clavien-Dindo classification system.

1 Background

1.1 Epidemiology

Gastric cancer is a significant health problem, being the fourth most common cancer and the third leading cause of cancer-related death worldwide. Age-standardized mortality rates for gastric cancer are 14.3 per 100 000 in men and 6.9 per 100 000 in women. Incidence shows clear regional and sex variations-rates are highest in Eastern Asia, Eastern Europe, and South America and lowest in Northern and Southern Africa. More than 679 000 new cases and 498,000 deaths occur every year in China, and an increasing trend of proximal gastric cancer is observed during the past years. In addition, SEER (Surveillance, Epidemiology, and End Results) show that the incidence of adenocarcinoma at the upper third of the stomach has increased four times over the past three decades, with a rate that has exceeded that at any other site of stomach.

1.2 Total Gastrectomy

1.2.1 Resection Range

Total gastrectomy generally refers to resection of lower esophagus, stomach, and duodenum bulb. The resection range is determined according to the primary tumor location. According to Japanese gastric cancer treatment guidelines 2014 (ver. 4), a sufficient resection margin should be ensured when determining the resection line in gastrectomy with curative intent. A proximal margin of at least 2 cm is recommended for T1 tumors, 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (Bormann I and II), and 5 cm is recommended for those with infiltrative growth pattern (Bormann III and IV). When these rules cannot be observed, it is advisable to examine the proximal resection margin by frozen section, especially for the adenocarcinoma of esophageal-gastric junction.

1.2.2 Lymphadenectomy

Japanese gastric cancer treatment guidelines 2014 (ver. 4)

D1+ lymphadenectomy is indicated for cT1N0 non-cardia gastric cancers.

- D1+：No. 1-7. 8a. 9.11p

D2-10 lymphadenectomy is indicated for cT1N1 and cT2N0 non-cardia gastric cancers.

- D2-10：No. 1-7. 8a. 9. 11p. 11d. 12a

Although there is no consensus of lymphadenectomy for adenocarcinoma of the esophagogastric junction (EGJ), lymphadenectomy is recommended according to Japanese gastric cancer treatment guidelines 2014 (ver.4) as following:

No. 1. 2. 3. 7 lymph nodes dissection is indicated for cT1N0 and cT1N1 tumors;

No. 1. 2. 3. 7. 8a. 9. 11p. 11d. 19. 20 lymph nodes dissection is indicated for cT2N0 tumors.

1.3 Feasibility and Necessity of LTG Research

Radical gastrectomy is the only curative therapeutic option for gastric cancer. The data from Korea and China show that the early surgical complications rate is 12.9%-18.9% after open distal gastrectomy, and it is higher in patients who underwent total gastrectomy. The early morbidities and mortalities rate is 36% and 4.7% for patients who underwent open total gastrectomy in USA from 2005-2011. Many clinical researches from Eastern Asia support this conclusion.

Since Kitano performed the first laparoscopic distal gastrectomy in 1994, the application of this new technology has been more widely. The safety and efficacy of this method are also attracting extensive attention worldwide. Many large-scale, prospective, multicenter, randomized, controlled trials have been conducted in Japan (JCOG0912 and JLSSG0901), Korea (KLASS-01 and KLASS-02), and China (CLASS-01). These trials are all designed to evaluate the non-inferiority of laparoscopic-assisted distal gastrectomy to its open counterpart.

By contrast, the study of laparoscopic total gastrectomy was just started without any RCTs existing at this moment. The standardization of techniques for esophagojejunal anastomosis in total gastrectomy has been difficult even for experienced surgeons, so only few single-center or retrospective study verifying the safety and efficacy have been published at home and abroad. The early surgical complications rate in patients who underwent laparoscopic total gastrectomy is 19.0%

in Korea and 27.5% in China. Above all, there are no studies about the feasibility, safety, and efficiency of laparoscopy total gastrectomy for gastric cancer.

At present, Japan (JCOG1401), Korea (KLASS-03), and Netherlands (STOMACH) have planned or launched clinical studies on laparoscopic total gastrectomy. China is one of the countries with the highest incidence of gastric cancer and surgeons have accumulated extensive experience through CLASS-01 study. So, it is time for conducting the clinical research of the safety of laparoscopy total gastrectomy for gastric cancer.

2 Objective

This study aims to determine the safety of LTG (Laparoscopic Total Gastrectomy) compared with OTG (Open Total Gastrectomy) for clinical stage I (T1N0M0、T1N1M0、T2N0M0) gastric adenocarcinoma located in gastric body, fundus, and esophagogastric junction.

To evaluate whether the morbidity and mortality of laparoscopic total gastrectomy are consistent with open total gastrectomy which are considered as traditional standard therapeutic patterns.

3 Design

A prospective, multicenter, randomized, controlled, open, non-inferiority verification design

3.1 Multicenter

Fourteen centers from Beijing, Shanghai, Guangzhou, Chengdu, Fuzhou, Nanjing and so on jointly participated in this study.

3.2 Grouping and Control

- Group A (study group): Laparoscopic total gastrectomy
- Group B (control group): Open total gastrectomy

3.3 Sample Size

It is a non-inferiority verification study on clinical safety, with the early operative morbidity and mortality rate as the main index for safety evaluation. According to the previous reports, the morbidity rate is about 20% and 15% for OTG group and LTG group, respectively.

Setting on-side $\alpha = 0.025$, $\beta = 0.2$, non-inferiority margin = 10%, assuming that laparoscopic surgical morbidity is 15%, while open surgical morbidity is 20%:

$$H_0 : \pi_1 \geq \pi_2 + \Delta \qquad H_1 : \pi_1 < \pi_2 + \Delta$$

Sample size for every group:

$$n = \frac{(Z_\alpha + Z_\beta)^2 \left[\pi_1(1-\pi_1) + \pi_2(1-\pi_2)\right]}{(\pi_2 + \Delta - \pi_1)^2} = \frac{(1.96 + 0.84)^2 \left[0.15(1-0.15) + 0.2(1-0.2)\right]}{(0.2 + 0.1 - 0.15)^2} = 100$$

Every group will need 100 cases. With the drop out rate is 10%, the final sample size is 112 cases for each group.

Case Allocation Form

Research Center	Number	LATG	OTG	Case Number
Zhongshan Hospital, Fudan University	01			
Beijing Cancer Hospital	02			
The First Hospital Affiliated to AMU	03			
Fudan University Shanghai Cancer Center	04			
Fujian Medical University Union Hospital	05			
The First Affiliated Hospital of Fujian Medical University	06			
Guangdong General Hospital	07			
The First Hospital of Jilin University	08			
Nangfang Hospital	09			
The First Affiliated Hospital with Nanjing Medical University	10			

Renji Hospital	11			
West China Hospital	12			
Chinese PLA General Hospital	13			

3.4 Randomization

In this study, the central dynamic, stratified randomization method is adopted, and the factors including age, gender, BMI, and investigators, are considered. After each case is enrolled, the research center will arrange the research assistant to send the information of included cases (age, gender, and BMI) to the data center through email, telephone, and SMS, etc. After analyzing the case information by the center randomization department, the case grouping will be determined.

3.5 Blind Method

Open design is adopted in this study.

3.6 Study Cycle

Case grouping cycle: Complete the enrollment within 18 months in the 14 centers.

Follow-up period: The inclusion of the first case is used as the starting point of the follow-up, while 30 days after operation (postoperative hospital stay≤30 days) or operation to first discharge from hospital (postoperative hospital stay＞30 days) of the last case is determined as the endpoint of follow-up.

4 Research Subjects

Patients that meet all the inclusion criteria and are beyond any one of exclusion criteria are eligible for this study.

4.1 Inclusion Criteria

- Aged 18-75 years
- Primary lesion is pathologically diagnosed as gastric adenocarcinoma
- Clinical stage IA (T1N0M0) or IB (T1N1M0, T2N0M0) according to AJCC-7th TNM staging system
- Tumor located in the upper or middle third of the stomach
- No invasion to Z-line
- Curative resection is expected to be achievable by total gastrectomy with D1+/D2 lymphadenectomy
- BMI < 30 kg/m^2
- ECOG PS 0 or 1
- ASA class: I, II, or III
- Sufficient organ functions
- Written informed consent

4.2 Exclusion Criteria

- Preoperative examination indicate enlargement of perigastric or retroperitoneal lymph nodes(≥1.0cm)
- Preoperative neoadjuvant chemotherapy or radiotherapy
- Previous history of upper abdominal surgery (except for laparoscopic cholecystectomy)
- Women during pregnancy or breast-feeding
- Synchronous or metachronous (within 5 years) malignancies
- Body temperature ≥ 38℃ before surgery or infectious disease with a systemic therapy indicated
- Severe mental disease
- Severe respiratory disease
- Severe hepatic and renal dysfunction
- Unstable angina pectoris or history of myocardial infarction within 6 months
- History of cerebral infarction or cerebral hemorrhage within 6 months
- Continuous systemic steroid therapy within 1 month (except for topical use)

- Gastric cancer complications (bleeding, perforation, obstruction) that requiring emergency surgery
- Patients are participating or have participated in another clinical trial (within 6 months)

4.3 Withdraw Criteria

- Confirmed that the stage of the disease is stage IV intraoperatively/postoperatively including positive peritoneal cytology examination;
- Confirmed that it is unable to complete R0 resection due to the disease progression intraoperatively;
- Confirmed that there are obviously enlargement of splenic hilar lymph nodes intraoperatively;
- Confirmed that it only need to perform distal gastrectomy intraoperatively;
- Patients requiring simultaneous surgical treatment for other diseases (except cholecystolithiasis);
- Sudden severe comorbidities in the perioperative period (intolerable surgery or anesthesia), which are unsuitable or unable to implement the treatment protocol of this study as schedule;
- Patients are confirmed to require emergency surgery according to the condition changes by attending doctors after included in this study;
- Patients are voluntary to quit or discontinue treatment due to personal reasons in any stage after included in this study;
- Treatment that proved to violate the study protocol.

4.4 Case Selection

(1) When admitted to hospital, patients should meet: aged 18-75 years; BMI＜30 kg/m^2; preoperative performance status (ECOG) of 0 or 1; women not during pregnancy or breast-feeding; no history of upper abdominal surgery (except for laparoscopic cholecystectomy); no prior treatment of chemotherapy, radiotherapy, targeted therapy, immunotherapy, etc.; no synchronous or metachronous (within 5 years) malignancies; no severe mental disease; no severe respiratory disease; no severe hepatic and renal dysfunction; no unstable angina pectoris or history of

myocardial infarction within 6 months; no history of cerebral infarction or cerebral hemorrhage within 6 months; no continuous systemic steroid therapy within 1 month (except for topical use); no diseases requiring simultaneous surgical treatment; pulmonary function test FEV1≥50% of the expected value.

(2) Primary lesion is pathologically diagnosed as gastric adenocarcinoma, such as papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, poorly cohesive carcinoma (including signet ring cell carcinoma and other variants), and mixed adenocarcinoma. Endoscopic ultrasonography (EUS) should be considered if available.

(3) The total abdominal and pelvic enhanced CT did not discover the enlargement of lymph nodes in the perigastric area (minor axis≥1 cm) or distant metastasis.

(4) Patients is explicitly diagnosed as cStage I gastric adenocarcinoma, and it is expected to obtain the R0 surgical results through undergoing total gastrectomy, D1+/D2-10 lymphadenectomy (also indicate to the multiple primary cancer).

(5) Patients did not receive any neoadjuvant chemotherapy or radiotherapy previously, and the attending doctor did not recommend them to do it.

(6) Preoperative ASA (American Society of Anesthesiologists) scoring: I-III;。

(7) No emergency surgery required.

(8) Now, the patients are the potentially eligible cases and then enter the **8.1 Case Inclusion Procedure**.

5 Endpoints

5.1 Primary Endpoint

- Early operative morbidity and mortality rate [Time frame: 30 days after operation (postoperative hospital stay ⩽ 30 days) or operation to first discharge from hospital (postoperative hospital stay > 30 days)]

5.2 Secondary Endpoint

- Postoperative recovery course [Time frame: Operation to first discharge from hospital]
- Postoperative hospital stay [Time frame: Operation to first discharge from hospital]

6 Diagnostic Criteria

- AJCC-7th TNM tumor staging system is adopted in this study;
- Classification of gastric adenocarcinoma: According to the international diagnostic criteria in histopathology, it is divided into papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, poorly cohesive carcinoma (including signet ring cell carcinoma and other variants), and mixed adenocarcinoma;
- cStage I：T1N0M0、T1N1M0、T2N0M0。

7 Qualification of the Responsible Surgeons

7.1 Basic Principle

The responsible surgeons should meet the following qualifications:

- Completing at least 50 cases of OTG and LTG with D2 lymphadenectomy respectively;
- Passing the blind review of surgery video.

7.2 Specific Measures

- The written documentation of the number of completed cases should be provided by the medical record room of the research centers.
- Blind review of surgery video: The applicants should provide the videos of OTG and LTG in recent one month (three cases each) to the CLASS Research Council; CLASS Research Council will select two videos of OTG and LATG separately, and randomly appoint three experts to peer review blindly. When three experts unanimously approved it, the applicant will be permitted to participate in this study as a researcher.

8 Standard Operation Procedures (SOP)

8.1 Case Selection

8.1.1 Assessment Item

The clinical examination results that got between hospital admission and study enrollment (usually 1 week) are determined as the baseline data. These data must include:

1) General status: height, weight, ECOG performance score, ASA score;
2) Peripheral venous blood: Hb, RBC, WBC, LYM, NEU, NEU%, PLT;
3) Blood biochemical indexes: ALB, prealbumin, TBil, DBil, AST, ALT, Cr, BUN, BG, CRP, HbA1c, Glycated albumin;
4) Serum tumor markers: AFP, CEA, CA19-9, CA12-5, CA72-4;
5) Total abdominal and pelvic enhanced CT (slice thickness of 10mm or less. If patients are allergic to the contrast agent, plain CT is permitted);
6) Upper gastrointestinal endoscopy and pathological examination; Endoscopic ultrasonography (EUS) should be considered if available;
7) Chest X-ray: cardiopulmonary conditions;
8) Standard 12-lead electrocardiogram;
9) Pulmonary function examination: FEV1, FVC.

8.1.2 Selection Application

Before enrollment in this study, the research assistant of each research center should fill in the [Eligibility Application Form] for patients that meet all the inclusion criteria and are beyond any one of exclusion criteria and then send it to the CLASS Research Committee through e-mail or fax for reviewing whether the patients are eligible.

8.1.3 Eligibility Consulting

Contact Information and Working Hours of CLASS Research Committee:

Add: CLASS Research Committee, Zhongshan Hospital, Fudan University

Tel: 021-64041990

Fax: 021-64038472

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

Contact Information:

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Code: 200032

Mobile: 15021383022

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8.1.4 Attentions

(1) The application and confirmation of eligibility should be completed preoperatively; any application during operation or postoperatively will not be accepted.

(2) [Eligibility Application Form] must be completely filled; otherwise, it will not be accepted.

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

(4) The research assistant of each center is responsible for the [eligibility confirmation notice] keeping.

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

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

(7) In case of repeat selection or incorrect registration, the research assistant of each research center should contact the CLASS Research Committee and record it.

8.2 Preoperative Management

- After obtaining the eligibility, a surgery should be performed within one week (including the 7th day).
- In case of deterioration of the disease before the expected day of surgery, whether to undergo

an elective surgery as planned should be determined by the doctor in charge; if an emergency surgery is required, the case should be withdrawn from PP set according to 4.3 Withdrawal Criteria.

- Patients with nutritional risk need preoperative enteral/parenteral nutritional support.
- For aged, smoking, and high-risk patients with diabetes, obesity, chronic cardio-cerebrovascular disease, or thromboembolic medical history, etc., the perioperative prophylaxis with low-molecular-weight heparin, anti-thrombotic compressing stockings, active lower limb massage, respiratory function training, and other preventive measures are recommended. Treatment for other potentially high-risk complications is not specified in this study protocol. The doctor in charge could decide the treatment method according to the clinical practice and record it in the CRF.
- According to the Japanese gastric cancer treatment guidelines 2014 (ver. 4), each research center should implement the total gastrectomy and D1+/D2-10 lymphadenectomy. The digestive tract reconstruction methods should be determined by the doctor in charge according to their experience and the specific intraoperative circumstances. Roux-en-Y reconstruction is recommended, and laparoscopy-assisted or total laparoscopy digestive tract reconstruction is both acceptable.
- The preoperative fasting, water deprivation, and other requirements before anesthesia should follow the conventional anesthesia scheme of each research center, which is not specified in this study.
- The principle of appropriate use of prophylactic antibiotics: the first dose of antibiotics should be administrated intravenously 30 minutes prior to surgery, the second generation of cephalosporin antibiotics are recommended (no brand is specified in this study); the preparation, concentration, and infusion rate of prophylactic antibiotics should comply with the clinical routines; prophylactic antibiotics are administrated no more than 3 days after surgery; the frequency is 1 time per 12 hours; if allergic to cephalosporin antibiotics (including history of allergy or allergy after administered), other types of antibiotics are permitted according to the clinical situation with the same requirements as cephalosporin antibiotics.

8.3 Randomized Grouping

- The study adopted the central dynamic, stratified randomization method.
- When receive the [eligibility confirmation notice], the research assistant of each research center should send the information of included cases (age, gender, and BMI) to the randomization department of data center.
- The randomization department of data center will determine the group of each case after analyzing the information, and then send the notice to the research center.
- The research assistant of each research center should timely receive the notice, and arrange the subjects into Group A or Group B in accordance with the grouping situation.

8.4 Standardization of Operation Practice

8.4.1 Handling Principles

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 depends on the anesthetist, which is not specified in this study.

8.4.1.2 Peritoneal Cytology

The peritoneal cytology examination should be first taken after entering the abdominal cavity. (Detailed procedures: take ascites (if any) after laparotomy; if there are no ascites, slowly inject 200-300ml physiological saline into the abdominal cavity; collect the fluid in the pelvic cavity, and send for examination).

8.4.1.3 Intraoperative Exploration

After the peritoneal cytology examination, the surgeon should explore the abdominal cavity to determine if there is any regional invasion or distant metastasis, including hepatic, peritoneal, mesenteric, or pelvic metastasis.

8.4.1.4 Regulations on Gastrectomy

Total gastrectomy must be performed according to the following oncological principles:

- To perform total gastrectomy according to the Japanese Gastric Cancer Treatment Guideline (Fourth edition, May. 2014).
- Requirements of surgical margin: A proximal margin of at least 2 cm is recommended for T1 tumors, 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (Bormann I and II), and 5 cm is recommended for those with infiltrative growth pattern (Bormann III and IV). When the rule cannot be observed, it is advisable to examine the proximal resection margin by frozen section. The distal margin located in the duodenal bulb.

8.4.1.5 Regulations on Lymphadenectomy

- To perform D1+/D2-10 lymphadenectomy according to the Japanese Gastric Cancer Treatment Guideline (Fourth edition, May. 2014).
- To perform D1+/D2-10 lymphadenectomy according to **1.2.2 Lymphadenectomy**.
- The names of relevant blood vessels are shown in the following table.

Total gastrectomy, D1+/D2-10 lymphadenectomy	No.
Right paracardial LNs,	1
Left paracardial LNs	2
LNs along the lesser curvature	3
LNs along the short gastric vessels	4sa
LNs along the left gastroepiploic vessels	4sb
LNs along the 2nd branch and distal part of right gastroepiploic vessels	4d
Suprapyloric LNs	5

Infrapyloric LNs	6
LNs along the trunk of left gastric artery	7
LNs along the common hepatic artery (Anterosuperior group)	8a
LNs around the celiac artery	9
LNs along the splenic artery (proximal, distal)	11p、11d
LNs in the hepatoduodenal ligament (along the proper hepatic artery)	12a
Infradiaphragmatic LNs	19
LNs in the esophageal hiatus of the diaphragm	20

8.4.1.6 Regulations on Omentum Majus Resection

This study protocol does not require performing the total omentum majus resection.

8.4.1.7 Regulations on Omental Bursa Resection

This study protocol does not require performing the total omental bursa resection.

8.4.1.8 Regulations on Digestive Tract Reconstruction

The digestive tract reconstruction methods should be determined by the doctor in charge according to their experience and the specific intraoperative circumstances. Roux-en-Y reconstruction is recommended. If surgical stapler is applied, whether the manual reinforced stitching to be performed on anastomotic stoma is determined by the doctor in charge, which is not specified in this study protocol.

8.4.1.9 Regulations on surgery-related Equipment and Instruments

Energy equipment, vascular ligation methods, and digestive tract anastomotic stapler are determined by the doctor in charge according to their experience and actual needs, which is not specified in this study protocol.

8.4.1.10 Regulations on Stomach Tube and Peritoneal Drainage Tube

Whether the stomach tube and peritoneal drainage tube to be indwelled or not after operation

is determined by the doctor in charge of each research center respectively according to their experience and actual needs, which is not specified in this study protocol.

8.4.1.11 Regulations on Performance of Other Concurrent Operations

If any other diseases are found during operation, the doctor in charge and the consultants of relevant departments should codetermine whether to have the necessity to perform homochronous operation. The priority of operations is determined according to clinical routine. However, the patients will be excluded from PP Set (except for cholecystectomy) according to **4.3 Withdraw Criteria**.

8.4.1.12 Regulations on Excluded Patients

After the doctor in charge confirms that the patient belongs to the eliminated case group, the research has to suspend immediately. The doctor in charge should decide subsequent treatment according to the clinical routine of the research center. Whether the laparoscopic surgery converses to laparotomy is determined by the doctor in charge; such subsequent treatments are not specified in this study protocol.

8.4.1.13 Regulations on Photograph

A digital camera with 8 million pixels at least will be used to take photographs that must include the following contents:

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

- Left gastroepiploic vessels region (1 pic), including the broken ends of left gastroepiploic vessels.
- Inferior pylorus region (1 pic), including the broken ends of right gastroepiploic vessels.
- Right region of superior margin of pancreas (1 pic), including the superior in front of common hepatic artery, the lower half of proper hepatic artery, the broken end of right gastric artery, and left part of portal vein (D2-10).
- Left region of superior margin of pancreas (1 pic), including the broken ends of left gastroepiploic vessels, the celiac artery, the proximal splenic artery, and the distal splenic

artery (D2-10).

- Esophageal hiatus region (1 pic), including the diaphragmatic crura, and the esophago-jejunal anastomosis.

(2) Skin incision closed (1 pic, with a ruler for reference).

(3) Postoperative fresh specimens (4 pics, with a ruler for reference)

1 pic before dissection and 3 pics after dissection along the greater curvature with a ruler for reference including 1 pic of the distance between the tumor edge and the proximal resection margin, 1 pic of the distance between the tumor edge and the distal resection margin, and 1 pic of the appearance of tumor after extension.

8.4.1.14 Regulations on Privacy Protection and Nomenclature of Photograph

- All image data must not disclose the personal privacy of patients.
- When the images are reviewed, the personal information must be hidden.
- The regions are marked with unified Chinese names: inferior pylorus region, the broken ends of left gastroepiploic vessels, right region of superior margin of pancreas, left region of superior margin of pancreas, esophageal hiatus region, incision, and specimen's observation (explanation should be annotated under pictures).

Examples:

- Photo Name: [Lap-subject's random number. The broken ends of left gastroepiploic vessels]/[Open-subject's random number. The broken ends of left gastroepiploic vessels]
- Filename: [Lap-subject's random number] / [Open-subject's random number]

8.4.1.15 Operation Quality Assurance

- To ensure the rationality of the surgical procedure, the quality of lymphadenectomy, the length of incision, and the integrity of specimen, a series of photographs of surgery are taken for assessment. The laparoscopic surgery procedure will be recorded, and unedited video files will be saved.
- The CLASS Research Committee will monitor and review regularly to ensure the quality of

operation.

8.4.1.16 Data Preservation

- All photographs will be saved in the hard disk and submitted to CLASS data center within one week after the operation. All research centers can back up their data of photographs and save their videos of laparoscopic surgery, respectively.
- If the research center cannot provide the photographs according to **8.4.1.13 Regulations on Photograph**, the surgery quality is unqualified and will be recorded by the CLASS Research Committee. This case still belongs to PP Set.

8.4.2 Regulations on Laparoscopy

The brands of laparoscopic apparatus, pneumoperitoneum apparatus, energy equipment, trocar, and image storage device are not specified in this study.

8.4.2.1 Regulations on Pneumoperitoneum

- CO_2 pneumoperitoneum is used to maintain the intra-abdominal pressure at 10-15mmHg.

8.4.2.2 Regulations on Trocar and Auxiliary Incision

- The number of trocars used in operation should not exceed 6; the positions of trocar and auxiliary incision are not specified in this study.
- There should be only one auxiliary incision, and the length should be less than 10 cm.
- If the auxiliary incision needs to be longer than 10 cm, the doctor in charge should record the reasons in CRF.

8.4.2.3 Definition of Laparoscopic Approach

- The laparoscopic operations inside the abdominal cavity must be performed using laparoscopic instruments.
- Perigastric devascularization, lymph node dissection, and blood vessel ligation must be

performed using laparoscopic instruments.

- Gastrectomy and digestive tract reconstruction could be completed with open approach through auxiliary incision.

8.4.2.4 Regulations on the Transferring to Laparotomy

- It is necessary to transfer to laparotomy when intra-abdominal hemorrhage, organ damage, and other severe/life-threatening complications that are difficult to control under laparoscope occur during the operation.
- It is necessary to transfer to laparotomy when intraoperative complications caused by CO_2 pneumoperitoneum during the operation may threaten the patient's life determined by surgeon in charge and anesthesiologist.
- For the transferring caused by other technical or equipment reasons, the doctor in charge should record the causes.
- The incision length of the laparotomy is not specified in this study.
- The cases of the transferring to laparotomy will still be regarded as the cases of laparoscopic group and analyzed in ITT Set.
- The reasons for transferring to laparotomy must be clearly recorded in the CRF.
- It is defined as the case of the transferring to laparotomy in this study when the auxiliary incision length is greater than 10 cm.

8.4.2.5 Subsequent Treatment of Excluded Patients of the Laparoscopy Group

- Whether the excluded patients continue to accept the operation under laparoscope is determined by the doctor in charge according to clinical experience.

8.4.3 Observation Items during the Operation

The research assistant after operation should record the specific items:

(1) Name of doctor in charge;

(2) Operation starting time (min), Operation finishing time (min);

(3) Operation type, extent of lymphadenectomy, reconstruction method;

(4) Incision length (cm), number of trocars;

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

(6) Estimated blood loss during operation (ml);

(7) Volume of blood transfusion (defined as transfusion of red cell suspension or plasma, ml);

(8) Tumor position (U/M, greater/lesser curvature, anterior/posterior wall, circumferential or not, the position of the main tumor body should be recorded in order if the tumor is trans-regional);

(9) Tumor size (maximum and minimum diameter, mm);

(10) Invasion depth, distant metastasis (position);

(11) Proximal resection margin length (mm), distal resection margin length (mm), radical degree (R0/R1/R2);

(12) Intraoperative complications, including:

- Surgery-related complications: intraoperative hemorrhage (≥400ml) and injury: vascular damage causing extra blood loss and injury of gastrointestinal tract, liver, pancreas, spleen, and other vital organs;
- Pneumoperitoneum-related complications: hypercapnia, mediastinal emphysema, subcutaneous emphysema, aeroembolism, and respiratory and circulatory instability caused by pneumoperitonum;
- Anesthesia-related complication.

(13) Intraoperative death: regardless of any reason.

8.5 Postoperative Management

8.5.1 Prophylactic Use of Analgesics

- Continuous intravenous postoperative analgesia is allowable but not mandatory within 72 hours postoperatively. Its dose, type, and rate of infusion should be performed according to clinical routines and patient conditions. The repeated use of prophylactic analgesic is not

permitted 72 hours after surgery unless it must be used.

8.5.2 Fluid Infusion and Nutritional Support

- Postoperative fluid infusion (including glucose, insulin, electrolytes, vitamins etc.) or nutritional support (enteral/parenteral) is performed according to the experience of the doctor in charge and clinical routines, which is not specified in this study.
- After oral feeding, fluid infusion/ nutritional support should gradually reduce until stop.

8.5.3 Rehabilitation Management

- Management of incision, stomach tube, and abdominal cavity drainage-tube: Following the clinical routines.
- Recovery eating time and transition strategies of diet: Following the clinical routines.

8.5.4 Discharge Standard

- No postoperative complications, meeting “body temperature is less than 37”, “the pain can be tolerated”, and “more than 1/3 normal diet can be oral intake”, a patient can be arranged for discharge, which should be recorded in the CRF.

8.5.5 Postoperative Observation Items

- Definition of postoperative “n days”: One day from 0:00 to 24:00. The time frame from the end of surgery to 24:00 of the surgery day is defined as “postoperative 0 day”; the next day from 0:00 to 24:00 is “postoperative 1 day”, and so on.
- From postoperative 1 day to discharge day, the research assistant should timely record the items. The observation items include:

(1) Pathological Results:

- Surgical outcomes (R0/R1/R2);
- Histological type of primary lesion, including papillary adenocarcinoma, tubular

adenocarcinoma, mucinous adenocarcinoma, poorly cohesive carcinoma (including signet ring cell carcinoma and other variants), and mixed adenocarcinoma;

- Histological grade (G1/G2/G3/G4/GX);
- Lauren classification (Intestinal/Diffuse/Mixed type);
- Lymphovascular invasion;
- Perineural invasion;
- Depth of stomach wall invasion;
- Total number of retrieved lymph nodes, number of lymph nodes in each group, number of lymph node metastasis in each group, and the total number of lymph node metastasis;
- Distant metastasis and sites (including positive peritoneal cytology).

□

(2) Early postoperative complications:

- Time frame: 30 days after operation (postoperative hospital stay ≤ 30 days) or operation to first discharge from hospital (postoperative hospital stay > 30 days).
- Observation items:

  ①Surgery-related complications：Wound complications (infection, effusion, dehiscence, poor healing, etc.), intra-abdominal active bleeding, digestive tract active bleeding, anastomotic stenosis, intestinal fistula, pancreatic fistula, chylous fistula, intra-abdominal abscess formation, gastroparesis, intestinal paralysis, intestinal obstruction, cholecystitis, pancreatitis, etc.

  ② System-related complications: Pneumonia, pleural effusion, pulmonary embolism, cardio-cerebrovascular complications (including thrombosis and embolism), deep venous thrombosis, urinary tract complications, catheter-related complications, etc.
- Classification of Surgical Complications (Clavien-Dindo Classification）

Grade I: Any deviation from the ordinary postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.

Grade III: Requiring surgical, endoscopic or radiological intervention

IIIa: Intervention not under general anesthesia

IIIb: Intervention under general anesthesia

Grade IV: Life-threatening complication (including CNS complications)* requiring IC/ICU management

IVa: Single organ dysfunction (including dialysis)

IVb: Multiorgan dysfunction

Grade V: Death of a patient

Suffix "d": If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to evaluate the complication fully.

* Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

IC: Intermediate care; ICU: Intensive care unit

(3) Blood test items (Postoperative day 1, 3, 5):

- Peripheral venous blood: Hb, RBC, WBC, LYM, NEU, NEU%, PLT;
- Blood biochemical indexes: ALB, prealbumin, TBil, DBil, AST, ALT, Cr, BUN, BG, CRP;

(4) Postoperative rehabilitation evaluation items:

- First ambulation time (hour);
- First anal exsufflation/ defecation time (hour);
- Time to full/semi-liquid food intake (hour);
- Daily highest body temperature (℃);
- Analgesia needed 72h after surgery (Y/N);
- Stomach tube extubation time (hour), daily gastric drainage volume (ml);
- Peritoneal drainage tube extubation time (hour), daily drainage volume (ml);
- Volume of blood transfusion (defined as transfusion of red cell suspension or plasma, ml));
- Hospitalization time after operation (d).

8.6 Follow-up

8.6.1 Follow-up Period and Attentions

- Each research center should arrange a specialist to carry out the follow-up 30 days after operation (postoperative hospital stay ⩽ 30 days) or operation to first discharge from hospital (postoperative hospital stay > 30 days).
- In this study, it is recommended that the follow-up examination should be conducted in the research center or a tertiary hospital, and the specialist should record the results.
- The specialist should evaluate and record the recovery situation of patient through analyzing the examination results.
- If the patient refuses the follow-up according to the protocol, it will be recorded as a case of "lost to follow-up", and analyzed together with the cases meeting the study criteria at the end of the study (it will not be withdrawn from the PP Set).

8.6.2 Examination Items

(1) Physical Examination:

- The doctor in charge should conduct a physical examination at the time of follow-up, and be aware of the vital signs, abdominal signs, systemic superficial lymph nodes and so on.

(2) Blood test items:

- Peripheral venous blood: Hb, RBC, WBC, LYM, NEU, NEU%, PLT；
- Blood biochemical indexes: ALB, prealbumin, TBil, DBil, AST, ALT, Cr, BUN, BG；
- Serum tumor markers: AFP, CEA, CA19-9, CA12-5, CA72-4；

(3) Imageological Examination:

- Total abdominal and pelvic enhanced CT (slice thickness of 10mm or less. If patients are allergic to the contrast agent, plain CT is permitted);
- Chest X-ray (post-anterior position and lateral position);
- Upper gastrointestinal tract iodine imaging;
- Others: gastroscopy, ultrasonography, whole-body bone scan, PET-CT, etc., when attending

doctors evaluate that it's necessary.

8.7 Postoperative Adjuvant Therapy

- According to the postoperative pathological results, R0 resection cases with Stage II/III/IV should be given adjuvant chemotherapy. The chemotherapy regimen is not specified in this study.
- For relapse cases after surgical resection, the follow-up treatment protocols are not specified in this study.

8.8 Definitions

8.8.1 ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group:

- 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 housework, office work.
- 2：Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
- 3：Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
- 4：Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
- 5：Dead.

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

8.8.2 ASA Classification

- ASA I: A normal healthy patient.
- ASA II: A patient with mild systemic disease.

- ASA III: A patient with severe systemic disease.
- ASA IV: A patient with severe systemic disease that is a constant threat to life.
- ASA V: A moribund patient who is not expected to survive without the operation.
- ASA VI: A declared brain-dead patient whose organs are being removed for donor purposes.

*The addition of “E” denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

Generally, ASA I/II patients are considered to be suitable for surgical treatment. ASA III patients are exposed to have some risks of anesthesia, and adequate preparation should be made before anesthesia. ASA IV patients are exposed to have high risks of anesthesia, and the perioperative mortality rate is very high even if the preoperative preparation is adequate. ASA V/VI patients are considered to be unsuitable for surgical treatment.

8.8.3 Oncology-related Definitions

In this study, tumor staging is based on the AJCC-7th TNM staging system. The principle of surgical treatment follows the Japanese Gastric Cancer Treatment Guideline (4th edition, May. 2014), and other writing and recording principles follow the Japanese Classification of Gastric Carcinoma (14th).

8.8.3.1 Primary Tumor 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, duodenum infiltration are respectively recorded as E (esophagus), D (duodenum). If the lesions are located in two or more adjacent areas, it should be recorded in order of the main part of the lesions. The principle of the record should follow the Japanese classification of gastric cancer (ver 14).

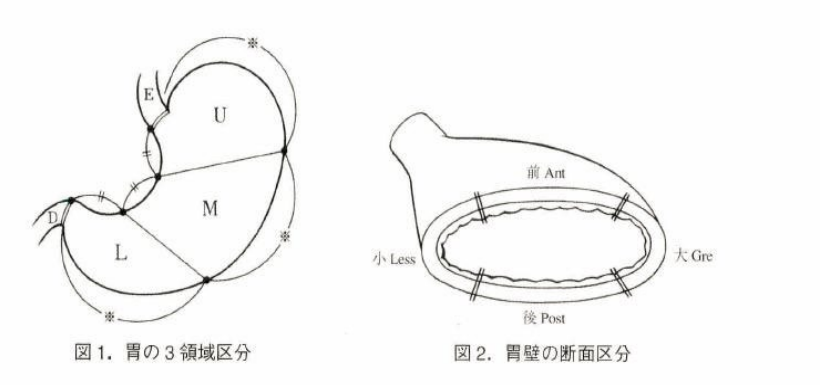

図 1．胃の 3 領域区分　　図 2．胃壁の断面区分

Fig.11 Partition of the stomach.

8.8.3.2 Tumor Staging Classification

8.8.3.2.1 Principle

- It is divided into clinical staging and pathological staging involving T (invasion depth), N (regional lymph nodes), and M (distant metastasis). All the staging should be written in capital letters, with Arabic numerals indicating the degree. X will be used if it cannot be assessed.

Clinical Classification	Pathological Classification
Physical Examination Endoscopy, imaging diagnosis Biochemistry and biopsy examination	Pathological diagnosis of the endoscopic/surgical specimens Peritoneal cytology

8.8.3.2.2 Primary tumor invasion depth

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
- T1: Tumor invades lamina propria, muscularis mucosae, or submucosa

  T1a: Tumor invades lamina propria or muscularis mucosae

T1b: Tumor invades submucosa

- T2: Tumor invades muscularis propria
- T3: Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures.
- T4: Tumor invades serosa (visceral peritoneum) or adjacent structures

  T4a: Tumor invades serosa (visceral peritoneum)

  T4b: Tumor invades adjacent structures

8.8.3.2.3 Tumor Metastasis

(1) Regional lymph nodes

- NX: Regional lymph node(s) cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in 1 to 2 regional lymph nodes
- N2: Metastasis in 3 to 6 regional lymph nodes
- N3: Metastasis in 7 or more regional lymph nodes

  N3a: Metastasis in 7-15 regional lymph nodes

  N3b: Metastasis in 16 or more regional lymph nodes

(2) Distant metastasis

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Record the metastasis sites: peritoneum (PER), liver (HEP), lymph node (LYM), skin (SKI), lung (PUL), bone marrow (MAR), bone (OSS), pleura (PLE), brain (BRA), meninges (MEN), ovary (OVA), peritoneal cytology (CY), and others (OTH).

Note: The positive peritoneal cytology is recorded as M1.

8.8.3.2.4 TNM Staging Classification

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

8.8.3.3 Pathological Type and Histologic Grade

8.8.3.3.1 Pathological Type

- Papillary adenocarcinoma
- Tubular adenocarcinoma
- Mucinous adenocarcinoma
- Poorly cohesive carcinoma
- Mixed adenocarcinoma

8.8.3.3.2 Histologic Grade

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

8.8.3.4 Evaluation of Radical Degree

8.8.3.4.1 Cancer invasion on the resection margin

(1) PM: proximal margin

- PMX: Proximal margin involvement cannot be assessed

- PM(-): No proximal margin involvement
- PM(+): Proximal margin involvement

(2) DM: distal margin

- DMX: Distal margin involvement cannot be assessed
- DM(-): No distal margin involvement
- DM(+): Distal margin involvement

8.8.3.4.2 Radical degree

- RX: Cannot be assessed
- R0: No cancer at resection margins
- R1: Microscopic residual cancer (including positive peritoneal cytology)
- R2: Macroscopic residual cancer or M1

9 Definitions of End Points and Surgical Results

9.1 Morbidity Rate

- Denominator: Number of all patients undergoing surgical treatment (laparoscopic/open). Numerator: Number of patients with any intraoperative/postoperative complications.
  Morbidity rate = Numerator/ Denominator*100%.

- Intraoperative/postoperative complication standards refer to **8.4.3 Observation Items during the Operation (12)** and **8.5.5 Postoperative Observation Items (2)**.

9.2 Mortality rate

- Denominator: Number of all patients undergoing surgical treatment (laparoscopic/open). Numerator: Number of patients who died within 30 days after operation (postoperative hospital stay ≤ 30 days) or operation to first discharge from hospital (postoperative hospital

stay > 30 days)

Morbidity rate = Numerator/ Denominator*100%.

- Patients who died during the operation according to **8.4.3 Observation Items during the Operation (13)** and regardless of any reasons.

9.3 Determination of Surgical Results

9.3.1 Rehabilitation Indicators

9.3.1.1 Time to Anal Exsufflation and Full/Semi-Liquid Food Intake

- The time will be recorded in hours.
- Anal exsufflation on the day of surgery is not recorded.
- In the case of no anal exsufflation/full/semi-liquid food intake before the first discharge, the discharge time should be recorded as the time of anal exsufflation/full/semi-liquid food intake.
- The first time of anal exsufflation/full/semi-liquid food intake is subject to the patient report.

9.3.1.2 Highest Body Temperature

- The daily highest body temperature should be recorded at least 3 times each day.

9.3.1.3 Analgesia Needed 72 hours after Surgery (Yes/No)

- Whether analgesia needed after 72 hours after surgery should be recorded. If really needed, the doctor in charge should record the reason for analgesia use, the name, type, and administration method of analgesia, and the condition of pain after analgesia use.

9.3.2 Completion Rate of LATG

- Denominator: Number of all patients undergoing surgical treatment (laparoscopic/open).

  Numerator: Number of patients undergoing LATG (No transferring to OTG).

  Completion rate = Numerator/ Denominator*100%.

9.3.3 Ratio of Conversion to Laparotomy

- Denominator: Number of all patients undergoing surgical treatment (laparoscopic/open).

  Numerator: Number of patients transferring from LATG to OTG regardless of any reason.

  Completion rate = Numerator/ Denominator*100%.

- It is defined as the case of the transferring to laparotomy in this study when the auxiliary incision length is greater than 10 cm.

10 Statistical Analyses

10.1 Definition of Analysis Set

- Intent-to-treat population (ITTP)

  Cases who agreed to participate in the clinical study and signed informed consent.

- Modified intent-to-treat population (MITTP)

  Cases randomly assigned to receive LATG or OTG and with at least one record of follow-up data after surgery.

- Per-protocol population (PPP)

  Cases accorded the study protocol, with good compliance, and completed CRF.

- Safety analysis population (SAP)

  Cases randomly assigned to receive LATG or OTG and with safety evaluation data after surgery.

10.2 Analysis Plan

- Statistical software: SAS statistical software.

- Descriptive statistics:
  - Measurement data: number of cases (number of missing cases), mean, median, standard deviation, P25, P75, minimum and maximum;
  - Enumeration data: frequency and the corresponding percentages. For primary safety endpoint, calculate the 95% CI in addition to the percentage.
- Statistical inference: unless otherwise specified, the two-sided P<=0.05 indicates statistically significant differences between the two groups.
  - Non-inferiority statistical inference for primary endpoint: if the upper limit of the 95% confidence interval (95%CI) for between-group difference calculated by Newcombe's method was less than 10%, it could be inferred that LTG was not inferior to OTG in the incidence of early complications.
  - Statistical analysis for baseline variables and secondary endpoints: continuous variables were examined by independent sample t-test or Wilcoxon rank-sum test, and categorical variables were compared by Pearson chi-square test, Fisher's exact test or CMH chi-square test as appropriate.
  - Analysis of withdrawn patients: the number of patients who are enrolled, withdrawn, removed, completed, and number of every analysis set will be listed.
- Stratified analysis for primary safety endpoint: Types of complications and The Clavien-Dindo classification system.

11 Data Management

11.1 Case Report Form (CRF)

11.1.1 Types and Submission Deadline

CRF used in this study and the submission deadline is as follows:

- Case screening: 7 days prior to surgery (time frame: 3 days)
- Enrolling: submitted to the data center one day prior to surgery

- Surgery: within 1 day after surgery
- Postoperation-Discharge: within 3 days after the first discharge
- Follow-up records: 7 days after each follow-up point

11.1.2 Transmission Methods

- Paper CRF and web-based ECRF form are used for data submission.

11.1.3 Amendment

After the start of the study, if the CRF is found lack of necessary data items or unclear items, 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 discussing at the meeting. If the amendment of the CRF does not require to modify the study protocol, this study protocol will not be modified. That whether it is necessary to submit a report or lodge an application to each research center's IRB for the CRF amendment should follow the provisions of various centers.

11.2 Monitoring and Supervision

In order to study whether the implementation follows the protocol safely, to study whether to collect the data correctly, monthly monitoring should be implemented during the period of selection of cases in principle. The monitoring is based on the hospital visit to compare the difference between and the original data and data submitted.

The periodic data report completed by the data center should be submitted to the Research Committee, the Research Responsible Person and Efficacy and Safety Evaluation Committee, and should be discussed and analyzed in accordance with relevant monitoring provisions. The regular monitoring is to aim at feedback, improving the scientific, 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 participating hospitals should strive to improve and to avoid the problems pointed out in the regular monitoring reports.

11.2.1 Monitoring Items

- Data collection completed status: Selected registration number (cumulative/different time of period, all hospitals/different hospitals)
- Eligibility: Ineligible patients/potentially ineligible patients (different hospitals)
- Different end of treatment, the reasons for suspension/end (different hospitals) in 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)
- Progress and safety of the study, other issues

11.2.2 Acceptable Range of Adverse Events

Based on the qualification of the research centers in this study, in general, treatment-related death and life-threatening complications caused by surgeries do not happen basically; the percent of more than 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 on each patient should be respectively reported to the 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 is up to 4, the final incidence proportion of adverse events will be apparently more than 3%, and

therefore the inclusion of patients must be immediately suspended. Whether the study can continue to proceed should be determined until reviewed by the CLASS Efficacy and Safety Evaluation Committee.

11.2.3 Deviation/Violation of Study Protocol

Surgical resection, clinical examinations, or toxicity, efficacy evaluation and so on failing to be conducted in accordance with the study protocol are the deviation of the study protocol. When the monitoring is carried out, deviations developed by the Data Center and Research Committee in advance (allowed to after the start of the study in special circumstances) beyond the acceptable range specified in each study center should be included in the monitoring report in the form of "cases of deviation possibility", and divided into any arbitrary one of the following after discussed by the Research Committee:

11.2.3.1 Violation

Clinically inappropriate, a deviation at least complying with one of the following items specified in the protocol is called "violation"

(1) Affecting the study endpoint evaluation

(2) The responsibility lays the doctor in charge/hospital

(3) Intentional or systematic

(4) Significant danger or the degree of deviation

Papers should record content violation in principle.

11.2.3.2 Acceptable deviation

- The acceptable deviation represents the acceptable range of each item set by the Research Representative/Committee and the data center before or after the beginning of the study.
- If it is within an acceptable range of deviation set in advance, no record is required in the monitoring report.

11.2.3.3 Deviation

- Items that do not comply with 11.2.3.1 or with 11.2.3.2 are deviation items.
- Specific deviations that occur several times should be recorded as much as possible when the paper is published.
- When the monitoring report is discussed, the deviation should be classified as the following:

  (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 by the doctor in charge/ hospital

12 Provisions on Adverse Events

The evaluation in this study refers to CTCAE v4.0 and "Accordion Severity Grading System"

12.1 Surgery-related Adverse Events

See the adverse events mentioned for surgical complications in **9 Definitions of End Points and Surgical Results**.

12.2 Evaluation

- Evaluation of adverse event/adverse reaction comprehensively refers to the [Accordion Severity Grading System] and [CTCAE v4.0].
- Adverse events are graded according to the content that is the nearest Grade 0 ~ 4 definition. For treatment-related death, death 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 the freedom registration column of the treatment process report, as well as Grade and the discovery date of Grade. The grade recorded in the treatment process report must be recorded in the case.

- CTCAE v4.0, 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 intervention. So it can be divided into two types based on whether there is a causal relationship or not.
- Therefore, even if events that “obviously caused by primary disease (cancer)” or caused by supportive therapy or combination therapy rather than the study regimen treatment (protocol treatment) are defined as “adverse events”.
- For adverse event data collection strategy, the following principle should be complied with in this study: Adverse events within 30 days from the last treatment day of the study regimen or hospitalization before first discharge (postoperative hospital stay > 30 days) (protocol treatment) should be collected entirely, regardless of the presence or absence of a causal relationship. (When adverse events are reported, the causality and classification of adverse events are separately discussed)

12.3 Reporting

- When “severe adverse events” or “unexpected adverse events” occur, the Research Responsible Person of each research center should report to the CLASS Research Committee/PI (Sun Yihong). Before the start of the study, the CLASS Research Committee should send the report template to each research center in advance. When “severe adverse events” or “unexpected adverse events” occur, the Research Responsible Person of each research center should report them to the CLASS Research Committee/PI (Sun Yihong).
- Adverse events based on the relevant laws and regulations should be reported to the province (city) Health Authority at the location of each research center. Severe adverse events based on clinical research-related ethical guidelines 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 each center should hold obligations 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 is the object that any adverse event should be reported urgently to:

- All patients died 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. If cases are withdrawn of treatment, even if the latter treatment has begun, those patients also belong to emergent reporting objects, as long as within 30 days from the last treatment day or during hospitalization (hospital stay > 30 days). (day 0 is the final treatment day and 30 days is starting from the next day)
- Those patients with unexpected Grade 4 non-hematologic toxicity (CTCAE v4.0 adverse events other than the blood/bone marrow group), having a causality with the treatment (any of definite, probable, possible) are also emergent reporting objects.

12.3.1.2 Adverse Events with Regular Reporting Obligations

Any one of the following adverse events is a regular reporting object:

(1) After 31 days from the last treatment day, death that cannot rule out the causal relationship with treatments, including suspected treatment-related death; death due to apparent primary disease is excluded.

(2) Expected Grade 4 non-hematologic toxicity (CTCAE v4.0 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 are found to bring essential and potentially permanent, significant impact on their offspring (except for MDS myelodysplastic syndrome, and secondary cancer)

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

12.3.2 Reporting Procedure

12.3.2.1 Emergency Reporting

- When emergent adverse events of emergency study reporting objects happened, the doctor in charge will quickly report it to the Research Responsible Person of the research participating hospitals. Where no contact can be gotten with the Research Responsible Person of the hospital, the coordinator, or the doctor in charge of the hospital must perform the responsibility instead.
- 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 fax 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 fax it to the CLASS Research Committee within 15 days after the occurrence of adverse events.

12.4 Responsibilities and Obligations

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

After the receipt of the report of the Research Responsible Person of the research

participating hospital, the CLASS Research Committee reply to the Research Responsible Person of the unit for confirmation and negotiation, and then they jointly determine the urgency, importance, and influence of reporting events; if necessary, they temporarily stop the study, and contact with all research participating hospitals to take emergency notification countermeasures. According to the severity of urgency, data center and research participating hospitals can be contacted by telephone or instrument FAX as soon as possible after the initial contact by phone.

12.4.2 Report to CLASS Efficacy and Safety Evaluation Committee

 After notifying, discussing and clarifying the adverse events in line with **12.3.1 adverse events with reporting obligations** in the emergency reports or regular reports to the Research Responsible Person of research participating units, the CLASS Research Committee should submit a report to the Efficacy and Safety Evaluation Committee within 3 days after the occurrence of adverse events and request a review that whether the reason analysis of and solution to the adverse events by the Research Responsible Person are appropriate..

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 the judgment of research continue/discontinue). 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 individual patient are included, but also consideration given to that whether the frequency of occurrence falls within the expected range are included. If the frequency of occurrence exceeds 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 notify the efficacy, and review, proposal content of the CLASS Efficacy and Safety Evaluation Committee in written form 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 written

form 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 the 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 no missing report by each research participating hospital. The existence or inexistence 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 raises the recommendations in written form for the Research Responsible Person, including whether to continue to enroll the study objects or whether to need to modify the study protocol.

13 Ethics

13.1 Responsibilities of Investigators

The investigators are responsible for the implementation of this study in its center. 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 especially noted that the investigators must ensure that subjects giving the written informed consent can be enrolled in this study only.

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 informed consent, the investigators will provide the information page of 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 words used must be fully, easily understood by non-professionals, so that they can sign on the informed consent form according to their willingness based on subjects' fully 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 on the informed consent form to prove that they agree to participate in the study. The signed informed consent form with signature and date should be kept in the research center where the investigators are located and must be properly safe kept for the future review at any time during the audit, inspection, inspection period. Before participating in the study, the subjects should provide a copy of signed and dated informed consent form.

At any time, as long as access to important new information that may be related to the consent of the subjects, the investigators will revise the information pages and any other written information provided to the subjects and re-submit them to the IEC/IRB for review and raising a favorable opinion. The revised information agreed will be provided to each subject participating in 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 with subject number (Allocation Number, AN). This number will represent the identity of the subject in the whole study and the clinical research database for the study. The collected data of subjects in the study will be stored in the ID.

In the entire study, various safety measures to minimize leaking risks in the utilization process of personal information will be taken, including: (1) only the investigators were able to link the research data of the subjects with themselves through the identify table kept in the research center after authorized; (2) in the raw data auditing on-site conducted by the supervisors of this study, as well as relevant inspection and inspection visit by the supervision departments, the personnel engaging above activities may view the original medical information of subjects that will be kept strictly confidential.

Data collection, transmission, handling, and storage of subjects will comply with the data protection and privacy regulations. This corresponding information will be provided to the subjects, and the subjects were asked to provide their consent for the treatment procedures of above data 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 opinion/approval documents of the IEC/IRB will be archived in the research center folders of the investigators.

Before obtaining the written proof of favorable opinions/approval of the IEC/IRB, the investigators are forbidden to begin the study in the center. The IEC/IRB will be asked to provide the written proof of the date of the favorable opinions/approval meeting and the written proof of the members presenting at the meeting and voting members. The IEC/IRB should provide the written proof of the favorable opinion/approval, recording the reviewed study, protocol version, and Informed Consent Form version. If possible, a copy of the minutes should also be obtained.

In the case of major revisions in this study, the amendment of the study protocol will be submitted to the IEC/ IRB prior to performing. 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 Supervisory 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

- Being responsible for developing study protocol, auditing eligibility for inclusion, and guiding the interpretation of informed consent; being responsible for the collection of hazardous/adverse event reports, guiding the clinical diagnosis and treatment of such events, and the emergency intervention of serious adverse events.
- The principle of CLASS Research Committee: Sun Yihong (Department of General Surgery, Zhongshan Hospital, Fudan University). Add: Department of General Surgery, Zhongshan Hospital, Fudan University, Fenglin Road 180, Shanghai 200032, China; Tel: 86-21-64041990; Fax: 86-21-64038472; Mobile: 13701735406; E-mail: sun.yihong@zs-hospital.sh.cn.
- Research Representative: Sun Yihong (Department of General Surgery, Zhongshan Hospital, Fudan University). Add: Department of General Surgery, Zhongshan Hospital, Fudan University, Fenglin Road 180, Shanghai 200032, China; Tel: 86-21-64041990; Fax: 86-21-64038472; Mobile: 13701735406; E-mail: sun.yihong@zs-hospital.sh.cn.
- Research centers assigned by the CLASS to participate in this study (hospital ranked in no particular order by region):

PI	Title	Research Center
Sun Yihong	Professor	Zhongshan Hospital, Fudan University
CI	**Title**	**Research Center**
Su Xiangqian	Professor	Beijing Cancer Hospital
Yu Peiwu	Professor	The First Hospital Affiliated to AMU
Huang Hua	Professor	Fudan University Shanghai Cancer Center
Huang Changming	Professor	Fujian Medical University Union Hospital
Ye Jianxin	Professor	The First Affiliated Hospital of Fujian Medical University
Li Yong	Professor	Guangdong General Hospital
Suo Jian	Professor	The First Hospital of Jilin University
Li Guoxin	Professor	Nangfang Hospital
Xu Zekuan	Professor	The First Affiliated Hospital with Nanjing Medical University
Zhao Gang	Professor	Renji Hospital
Hu Jiankun	Professor	West China Hospital
Du Xiaohui	Professor	Chinese PLA General Hospital

14.2 CLASS Efficacy and Safety Evaluation Committee

- Being responsible for the supervision, monitoring of the treatment safety, and therapeutic efficacy of this study.
- The principal of CLASS Efficacy and Safety Evaluation Committee: Sun Yihong (Department of General Surgery, Zhongshan Hospital, Fudan University)

14.3 CLASS Data Center

- Participating in the design of this study protocol, being responsible for data analysis, statistical interpretation, and issuing of statistical reports.

- Being 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 Zhao Naiqing (Department of Biological Statistics, Fudan University)
- The Second Person in Charge of Management of Study Data: CRO

14.4 Data and Safety Monitoring Board

- DSMB is responsible for the supervision of efficacy, the safety of this study, supervising of all aspects performed of the study, and licensing before the release of the validity of the study results.
- Person in Charge of DSMB: CRO

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

- Being Responsible for evaluating this study in order to determine “whether to minimize risks that the subjects are exposed to” and “whether the risks that the subjects are exposed to are reasonable compared to expected benefits”.
- The independent Ethics Committee/Institutional Review Board (IEC/IRB) at the location of each research center is responsible for the ethics review of all research participating units.

15 Publications of Research Results

- The publication of the research results of the paper should follow the established principle of the publication period in the study protocol.
- When there are no definite established policies of the research group, the publication of the paper should follow the following principle: the main statistical analysis, the final statistical analysis, and the final complete public paper written contributions to journals in English. Unless clearly provided in the study protocol, the methods of used statistical analysis and the

final statistical analysis cannot be published without approval of the Efficacy and Safety Evaluation Committee. However, excluding the results of the final statistical analysis of this study, the research representative or the Research Committee can publish the Society Paper (Abstract) to introduce of this study just need to obtain consent from the person in charge of the data center.

- In principle, the author of the main published paper of the research results is firstly the Research Committee, followed by the research representative, the person in charge of statistics of the data center (the person in charge of statistical analysis for publication). The rest should follow the paper written contribution rules. In order of the selected registration size of samples, the Research Responsible Persons of all research centers are listed as co-authors. All co-authors shall review the paper and agree to publish it before the paper submission. If the consent cannot be gotten from an investigator because of disagreeing with the published content, the research representative has the right not to list the investigator as co-author.
- For the overall data collected in this study, if any person in charge of research center need make a secondary analysis or make an analysis for other research purposes, the consent of the CLASS Research Committee shall be gotten; when a person in charge of research center need to use the data of his group to make the speech on the academic conference, the data source should be noted and informed the CLASS Research Committee.
- The publication of the primary objectives should be penned by people in charge of the research, principally. The publication of the second objectives or secondary analysis for the results can 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 the whole research.
- The person in charge of the research center has right to save their single-center data but should follow the privacy principles; For the results, form, the content of published single-center data, the relevant responsibilities should be at their own risk. The CLASS Research Committee does not assume any responsibility; the use of single-center data must be informed and obtain the recognized accuracy from the CLASS data center; the single-center data of statistical analysis must be marked to derive from this study of the

CLASS in order to avoid repeat inclusion at the time of systemic analysis.

- Without the approval of both the Research Committee and the data center, No Research Committee personnel cannot directly obtain the overall data and results of statistical analysis of this study from the data center.

16 References

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